

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) EP 1 310 493 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
17.08.2005 Bulletin 2005/33

(51) Int Cl.7: C07D 253/06, C07C 13/615,
A61P 37/00, A61P 11/06,
A61P 29/00, A61P 35/00

(21) Application number: 02257719.1

(22) Date of filing: 07.11.2002

(54) N-adamantylalkyl benzamide derivates as p2x7-receptor antagonists

N-Adamantylalkyl Benzamide Derivativen als p2x7-rezeptor antagonisten

Dérivés de la (N-adamantylalkyl)-benzamide comme antagonistes des récepteurs p2x7

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
IE IT LI LU MC NL PT SE SK TR

(30) Priority: 12.11.2001 US 336892 P

(43) Date of publication of application:
14.05.2003 Bulletin 2003/20

(73) Proprietor: Pfizer Products Inc.
Groton, Connecticut 06340 (US)

(72) Inventor: Duplantier, Allen J.,
Pfizer Global Res. & Dev.
Groton, Connecticut 06340 (US)

(74) Representative: Motion, Keith Robert et al
Pfizer Limited
Patents Department
Ramsgate Road
Sandwich, Kent CT13 9NJ (GB)

(56) References cited:

WO-A-00/61569 WO-A-01/44213
WO-A-01/94338 WO-A-99/29660
US-A- 3 789 072

• NARAYANAN V L: "ADAMANTYL ANALOGS OF
2'-(DIMETHYLAMINOPROPYLTHIO)CINNAMANI
LIDE" JOURNAL OF MEDICINAL CHEMISTRY,
AMERICAN CHEMICAL SOCIETY.
WASHINGTON, US, vol. 15, no. 11, 1972, pages
1180-1182, XP002938144 ISSN: 0022-2623

Remarks:

The file contains technical information submitted
after the application was filed and not included in this
specification

EP 1 310 493 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

[0001] The present invention relates to N-alkyl adamantyl triazinyl benzamide derivatives, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them, and their use in therapy. The active compounds of the present invention are useful in the treatment of inflammatory diseases such as osteoarthritis and rheumatoid arthritis; allergies, asthma, COPD, cancer, reperfusion or ischemia in stroke or heart attack, autoimmune diseases and other disorders. The active compounds are also antagonists of the P2X₇ receptor.

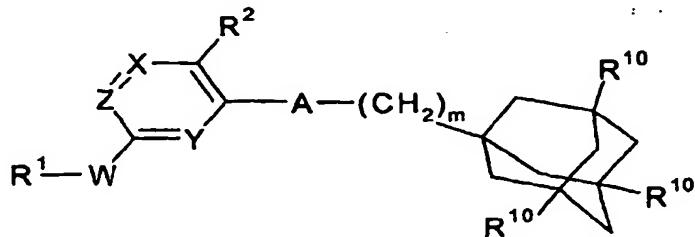
[0002] The P2X₇ receptor (previously known as P2Z receptor), which is ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1 β (IL-1 β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and proliferation (T cells), apoptosis and L-selectin shedding (lymphocytes). P2X₇ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes and mesangial cells.

[0003] P2X₇ antagonists are known in the art, such as International Patent Publications WO 01/46200, WO 01/42194, WO 01/44213, WO99/29660, WO 00/61569, WO 99/29661, WO 99/29686, WO 00/71529, and WO 01/44170.

[0004] Benzamides, heteroarylamides and reverse amides for uses other than inhibition of P2X₇ have been published, such as International Patent Publications WO 97/22600, EP 138,527, WO 00/71509, WO 98/28269, WO 99/17777 and WO 01/58883.

SUMMARY OF THE INVENTION

[0005] The present invention relates to a compound of the formula



wherein A is -(C=O)NH- or -NH(C=O)-; preferably -(C=O)NH-;

X, Y and Z are =(CR³)-, =(CR⁴)-, and =(CR⁵)-; or =N-, =(CR⁴)-, and =(CR⁵)-; or =(CR³)-, =N-, and =(CR⁵)-; or =(CR³)-, =(CR⁴)-, and =N-; or =N-, =(CR⁴)-, and =N-; or =(CR³)-, =N-, and =N-; or =N-, =N-, and CR⁵, respectively;

W is a bond, -O-, >(C=O), -(CH₂)_o, -(CH=CH)-, -C≡C-, -(CH₂)_oO-, -O(CH₂)_o-, -O(CH₂)_pO-, -C(CH₂)_qO(CH₂)_r-, -CR⁶(OH)-, -(CH₂)_pO(CH₂)_r, -(CH₂)_qO(CH₂)_oO, >NR⁷, -(CH₂)_oNR⁷-, -NR⁷(CH₂)_o-, -(CH₂)_pNR⁷(CH₂)_r-, -O(CH₂)_qNR⁷(CH₂)_r-, -(CH₂)_rNR⁷(CH₂)_qO-, -NR⁷(CH₂)_qO-, -NR⁷(CH₂)_qO(CH₂)_r-, -CONR⁷-, NR⁷CO-, >S(O)_n, -S(O)_nCH₂-, -CH₂S(O)_n-, -SO₂NR⁷-, or -NR⁷SO₂-,

m is an integer from 1 to 2;

n is an integer from 0 to 2;

o is an integer from 1 to 6;

p is an integer from 2 to 6;

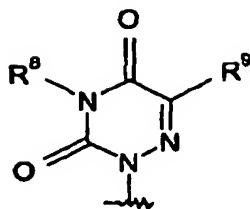
q is an integer from 2 to 3;

r is an integer from 1 to 3;

R¹ is the group

50

55



10

wherein R⁸ is selected from the group consisting of hydrogen, CF₃-, (C₁-C₆)alkyl, HO-(C₂-C₆)alkyl or (C₃-C₆)cycloalkyl group,

wherein R⁹ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, CF₃-CH₂-, HO-(C₂-C₆)alkyl or (C₃-C₆)cycloalkyl group;

15

R² is selected from the group of suitable substituents such as (i) hydrogen, (ii) halogen, (iii) cyano, (iv) (C₁-C₄)alkyl optionally substituted by one to four chloro or fluoro, (v) (C₂-C₄)alkenyl; (vi) (C₂-C₄)alkynyl and (vii) (C₁-C₄)alkyloxy optionally substituted by one to four chloro or fluoro;

20

R³, R⁴ and R⁵ are each independently selected from the group suitable substituents such as (i) hydrogen; (ii) halogen, (iii) cyano, (iv) nitro, (v) amino, (vi) hydroxyl, (vii) (C₁-C₆)alkyl optionally substituted by one to four chloro or fluoro, (viii) (C₃-C₆)cycloalkyl optionally substituted by one to four chloro or fluoro, (ix) (C₁-C₆)alkyloxy optionally substituted by one to four chloro or fluoro, and (x) (C₃-C₆)cycloalkyloxy optionally substituted by one to four chloro or fluoro;

R⁶ is hydrogen or (C₁-C₆)alkyl, preferably methyl;

R⁷ is hydrogen, (C₁-C₆)alkyl or (C₃-C₆)cycloalkyl;

each R¹⁰ is independently selected from the group consisting of hydrogen or halo;

25

or the pharmaceutically acceptable salts or solvates thereof.

25

[0006] The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula I. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-totuenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)]salts.

30

[0007] The invention also relates to base addition salts of formula I. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

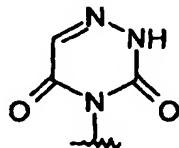
35

[0008] The compounds of this invention include all stereoisomers (e.g., cis and trans isomers) and all optical isomers of compounds of the formula I (e.g., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers.

40

[0009] The compounds, and salts of the present invention can exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the present invention. Tautomers exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the present compounds. One example of a tautomeric structure is a group of the formula

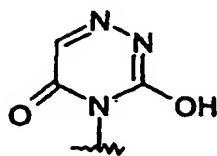
50



55

[0010] One skilled in the art will appreciate that this group can also be drawn as its tautomer

5



[0011] The present invention also includes atropisomers of the present invention. Atropisomers refer to compounds of formula I that can be separated into rotationally restricted isomers.

[0012] The compounds of this invention may contain olefin-like double bonds. When such bonds are present, the compounds of the invention exist as cis and trans configurations and as mixtures thereof.

[0013] As used herein, the term "alkyl," as well as the alkyl moieties of other groups referred to herein (e.g., alkoxy), may be linear or branched (such as methyl, ethyl, *n*-propyl, *isopropyl*, *n*-butyl, *iso*-butyl, *secondary*-butyl, *tertiary*-butyl); optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl. The phrase "each of said alkyl" as used herein refers to any of the preceding alkyl moieties within a group such alkoxy, alkenyl or alkylamino. Preferred alkyls include (C₁-C₄)alkyl, most preferably methyl and ethyl.

[0014] As used herein, the term "cycloalkyl" refers to a mono, bicyclic or tricyclic carbocyclic ring (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl and bicyclo[5.2.0]nonanyl, etc.); optionally containing 1 or 2 double bonds and optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl.

[0015] As used herein, the term "halogen" includes fluoro, chloro, bromo or iodo or fluoride, chloride, bromide or iodide.

[0016] As used herein, the term "halo-substituted alkyl" refers to an alkyl radical as described above substituted with one or more halogens included, but not limited to, chloromethyl, dichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trichloroethyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl.

[0017] As used herein, the term "alkenyl" means straight or branched chain unsaturated radicals of 2 to 6 carbon atoms, including, but not limited to ethenyl, 1-propenyl, 2-propenyl (allo), *iso*-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-but enyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl.

[0018] As used herein, the term "(C₂-C₆)alkynyl" is used herein to mean straight or branched hydrocarbon chain radicals having one triple bond including, but not limited to, ethynyl, propynyl, butynyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl.

[0019] As used herein, the term "carbonyl" or "(C=O)" (as used in phrases such as alkylcarbonyl, alkyl-(C=O)- or alkoxy carbonyl) refers to the joinder of the >C=O moiety to a second moiety such as an alkyl or amino group (i.e. an amido group). Alkoxy carbonyl amino (i.e. alkoxy(C=O)-NH-) refers to an alkyl carbamate group. The carbonyl group is also equivalently defined herein as (C=O). Alkyl carbonyl amino refers to groups such as acetamide.

[0020] As used herein, the term "aryl" means aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indanyl and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl.

[0021] As used herein, the term "heteroaryl" refers to an aromatic heterocyclic group usually with one heteroatom selected from O, S and N in the ring. In addition to said heteroatom, the aromatic group may optionally have up to four N atoms in the ring. For example, heteroaryl group includes pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiényl, furyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), quinolyl, isoquinolyl, benzothienyl, benzofuryl, indolyl, and the like; optionally substituted by 1 to 3 suitable substituents as defined above such as fluoro, chloro, trifluoromethyl, (C₁-C₆)alkoxy, (C₆-C₁₀)aryloxy, trifluoromethoxy, difluoromethoxy or (C₁-C₆)alkyl. Particularly preferred heteroaryl groups include oxazolyl, imidazolyl, pyridyl, thiényl, furyl, thiazolyl and pyrazolyl.

[0022] Nitrogen heteroatoms as used herein refers to N=, >N and -NH; wherein N= refers to a nitrogen double bond connection; >N refers to a nitrogen containing two bond connections and -N refers to a nitrogen containing one bond connection.

[0023] "Embodiment" as used herein refers to specific groupings of compounds or uses into discrete subgenera. Such subgenera may be cognizable according to one particular substituent such as a specific R¹ or R² group. Other

subgenera are cognizable according to combinations of various substituents, such as all compounds wherein R² is chloro and R¹ is optionally substituted 6-azauracil. The phrase "in combination with each of the aforementioned embodiments" refers to combinations of the identified embodiment with each embodiment previously identified in the specification. Thus an embodiment of compounds wherein R¹ is optionally substituted 6-azauracil "in combination with each of the aforementioned embodiments" refers to additional embodiments comprising combinations of the R¹ optionally substituted 6-azauracil embodiment with each embodiment previously identified in the specification.

5 [0024] A preferred embodiment of the present invention, referred to as the phenyl compounds, are those compounds of formula I wherein X, Y and Z are =(CR³)-, =(CR⁴)-, and =(CR⁵)-.

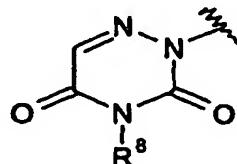
10 [0025] Another embodiment of the present invention are those compounds of formula I wherein one of R³, R⁴ or R⁵ is selected from the group consisting of (i) hydrogen (ii) halogen, (iii) nitro, (iv) amino, (v) hydroxyl, (vi) (C₁-C₆) alkyl optionally substituted by one to four chloro or fluoro, (vii) (C₃-C₆)cycloalkyl optionally substituted by one to four chloro or fluoro, (viii) (C₁-C₆)alkyloxy optionally substituted by one to four chloro or fluoro, and (ix) (C₃-C₆)cycloalkyloxy optionally substituted by one to four chloro or fluoro. A more preferred embodiment of the invention are those compounds of formula I wherein one of R³, R⁴ or R⁵ is selected from the group consisting of hydrogen, halogen, cyano, hydroxyl, (C₁-C₄)alkyl optionally substituted by one to four chloro or fluoro, and (C₁-C₄)alkyloxy optionally substituted by one to four chloro or fluoro. An even more preferred embodiment of the invention are those compounds of formula I wherein one of R³, R⁴ or R⁵ is selected from the group consisting of hydrogen, fluoro, cyano, methyl, -CF₃, methoxy and -OCF₃. Most preferably each of R³, R⁴ or R⁵ is hydrogen.

15 [0026] Another embodiment of the present invention are those compounds of formula I wherein m is one.

20 [0027] A preferred embodiment of the present invention, referred to the amide compounds or more specifically as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, and pyrazinamide compounds, are those compounds of formula I wherein A is -(C=O)NH-.

25 [0028] Another embodiment of the present invention, referred to as the reverse amide compounds or more specifically as the formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds, are those compounds of formula I wherein A is -NH(C=O)-.

30 [0029] Another preferred embodiment of the present invention, referred to as the 6-azauracil compounds, are those compounds of formula I (as well as the benzamide, nicotinamide, picolinamide, isonicotinamide, pyridazinamide, pyrimidinamide, pyrazinamide, formanilide, carboxaminopyridine, carboxaminopyridazine, carboxaminopyrimidine and carboxaminopyrazine groups of compounds) wherein R¹ is



40

wherein R⁸ is selected from the group consisting of hydrogen or (C₁-6)alkyl.

[0030] Another preferred embodiment of the present invention are those compounds of formula I wherein W is a bond.

45 [0031] Another embodiment of the present invention are those compounds of formula I wherein is -O-, -(CH₂)_oO-, -O(CH₂)_pO-, -(CH₂)_rO(CH₂)_qO-, >NR⁷, -(CH₂)_nNR⁷-, -O(CH₂)_pNR⁷-, -(CH₂)_rNR⁷(CH₂)_qO-, -NR⁷(CH₂)_pO-, -CONR⁷-, S(O)_n-, -CH₂S(O)_n-, -SO₂NR⁷-, or -NR⁷SO₂-,

n is 0, 1 or 2;

o is an integer from 1 to 6;

p is an integer from 2 to 6;

50

q is an integer from 2 to 3;

r is an integer from 1 to 3;

R⁷ represents hydrogen or (C₁-C₆)alkyl, preferably methyl;

[0032] Another embodiment of the present invention are those compounds wherein W is >(C=O), -(CH₂)_o-, -CH=, -O(CH₂)_p-, O(CH₂)_qO(CH₂)_r-, -CR⁶(OH)-, -(CH₂)_rO(CH₂)_r-, -O(CH₂)_qNR⁷(CH₂)_r-, -NR⁷(CH₂)_o-, -(CH₂)_rNR⁷(CH₂)_r-, -NR⁷(CH₂)_qO(CH₂)_r-, -NR⁷CO-, or -S(O)_nCH₂-;

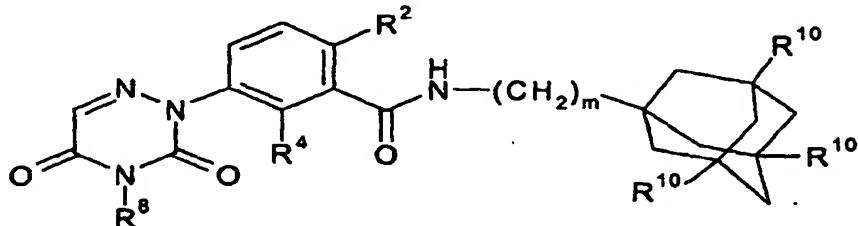
n is 0, 1 or 2;

o is an integer from 1 to 6;

p is an integer from 2 to 6;

q is an integer from 2 to 3;
 r is an integer from 1 to 3;
 R⁶ is hydrogen, (C₁-C₆)alkyl or (C₃-C₈)cycloalkyl; and
 R⁷ represents hydrogen or (C₁-C₆)alkyl, preferably methyl.

5 [0033] Another preferred embodiment of the present invention are those compounds of formula I wherein said compound of formula I has the formula



1a

20 wherein m is an Integer from 1 to 2;

R² is fluoro or chloro;

R⁴ is selected from the group consisting of hydrogen, halogen, cyano, hydroxyl, (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl, (C₁-C₃)alkyloxy, -CF₃, -OCF₃ and (C₃-C₆)cycloalkyloxy;

25 R⁸ is a hydrogen atom or a (C₁-C₆)alkyl, CF₃-CH₂-, HO-(C₂-C₆)alkyl or (C₃-C₈)cycloalkyl group;

R¹⁰ is hydrogen or fluoro;

or a pharmaceutically acceptable salt or solvate thereof.

[0034] Examples of specific preferred compounds of the formula I are the following:

30 N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide;
 N-Adamantan-1-ylmethyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-methyl-benzamide;
 2-Chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-N-tricyclo[4.3.1.1^{3,8}]undec-1-ylmethyl-benzamide;
 N-Adamantan-1-ylmethyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-fluoro-benzamide;
 N-Adamantan-1-ylmethyl-2-chloro-5-(4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide;
 35 2-Chloro-N-(3,5-difluoro-adamantan-1-ylmethyl)-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide; and
 N-(2-Adamantan-1-yl-ethyl)-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide.

[0035] Examples of other compounds of the formula I are the following:

40 2-Adamantan-1-yl-N-[2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-phenyl]-acetamide;
 2-Adamantan-1-yl-N-[5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-methyl-phenyl]-acetamide;
 N-[2-Chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-phenyl]-2-tricyclo[4.3.1.1^{3,8}]undec-1-yl-acetamide;
 2-Adamantan-1-yl-N-[5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-fluoro-phenyl]-acetamide;
 45 2-Adamantan-1-yl-N-[2-chloro-5-(4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-phenyl]-acetamide;
 N-[2-Chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-phenyl]-2-(3,5-difluoro-adamantan-1-yl)-acetamide;
 N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-nicotinamide;
 6-(3,5-Dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-3-methyl-pyridine-2-carboxylic acid (adamantan-1-ylmethyl)-amide;
 N-Adamantan-1-ylmethyl-2-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-5-fluoro-isonicotinamide; and
 50 5-Chloro-2-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-pyrimidine-4-carboxylic acid (tricyclo[4.3.1.1^{3,8}]undec-1-ylmethyl)-amide.

[0036] The present invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain

the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically-labelled compounds of Formula I of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically-labelled reagent for a non-isotopically-labelled reagent.

5 [0037] The compounds of Formula I or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of any disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated cytokine production by such mammal's cells, such as but not limited to monocytes and/or macrophages.

10 [0038] The present invention relates to a method for treating a P2X_7 mediated disease in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of formula I.

15 [0039] The present invention also relates to the use of a compound of formula I, in the manufacture of a medicament for treating a condition selected from the group consisting of arthritis (including psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and acute synovitis), inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, adult respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, allergic reactions, allergic contact hypersensitivity, eczema, contact dermatitis, psoriasis, sunburn, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, bone resorption disease, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, neurotrauma, spinal cord injury, neurodegenerative disorders, Alzheimer's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, corneal scarring, scleritis, abnormal wound healing, burns, autoimmune disorders, Huntington's disease, diabetes, AIDS, cachexia, sepsis, septic shock, endotoxic shock, conjunctivitis shock, gram negative sepsis, toxic shock syndrome, cerebral malaria, cardiac and renal reperfusion injury, thrombosis, glomerularonephritis, graft vs. host reaction, allograft rejection, organ transplant toxicity, ulcerative colitis, or muscle degeneration, in a mammal, including a human.

20 [0040] The present invention relates to a pharmaceutical composition for the treatment of a P2X_7 mediated disease in a mammal which comprises an effective amount of a compound according to formula I and a pharmaceutically acceptable carrier.

25 [0041] The present invention relates to a pharmaceutical composition for the treatment of a condition selected from the group consisting of arthritis (including psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and acute synovitis), inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, adult respiratory distress syndrome, asthma, bronchitis, chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, allergic reactions, allergic contact hypersensitivity, eczema, contact dermatitis, psoriasis, sunburn, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, bone resorption disease, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, neurotrauma, spinal cord injury, neuro-degenerative disorders, Alzheimer's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, corneal scarring, scleritis, abnormal wound healing, burns, autoimmune disorders, Huntington's disease, diabetes, AIDS, cachexia, sepsis, septic shock, endotoxic shock, conjunctivitis shock, gram negative sepsis, toxic shock syndrome, cerebral malaria, cardiac and renal reperfusion injury, thrombosis, glomerularonephritis, graft vs. host reaction, allograft rejection, organ transplant toxicity, ulcerative colitis, or muscle degeneration in a mammal, including a human, comprising an amount of a compound to formula I, effective in treating such a condition and a pharmaceutically acceptable carrier.

30 [0042] Preferably, the compounds of the invention are useful for the treatment of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, chronic obstructive pulmonary disease (COPD), hyperresponsiveness of the airway, septic shock, glomerulonephritis, Irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukemia, diabetes, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischemic heart disease, stroke and varicose veins.

35 [0043] The present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

[0044] In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

[0045] The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in the manufacture of a medicament for treating osteoarthritis.

5 [0046] The invention further provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in the manufacture of a medicament for effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, irritable bowel disease, atherosclerosis or psoriasis).

10 [0047] The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined, in the manufacture of a medicament for treating an obstructive airways disease (e.g. asthma or COPD).

[0048] The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

15 [0049] The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

[0050] The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

20 [0051] For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 1 mg to 1 gram, preferably 1 mg to 250 mg, more preferably 10 mg to 100 mg.

[0052] The present invention also encompasses sustained release compositions.

25 [0053] The present invention also relates to processes of preparing the compounds of formula I and intermediates used in such processes.

[0054] One of ordinary skill in the art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in the art will also appreciate that when using the compounds of the invention in the treatment of a specific disease that the compounds of the invention may be combined with various existing therapeutic agents used for that disease.

30 [0055] For the treatment of rheumatoid arthritis, the compounds of the invention may be combined with agents such as TNF- α inhibitors such as anti-TNF monoclonal antibodies (such as Remicade, CDP-870 and D₂E₇) and TNF receptor immunoglobulin molecules (such as Enbrel \circledR), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib) low dose methotrexate, lefunomide; ciclesonide; hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

35 [0056] The present invention still further relates to the combination of a compound of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist selected from the group consisting of zileuton; ABT-761; feneleuton; teponoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonarnides; 2,6-di-*tert*-butylphenol hydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2-cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

40 [0057] The present invention still further relates to the combination of a compound of the invention together with a receptor antagonists for leukotrienes LTB₄, LTC₄, LTD₄, and LTE₄ selected from the group consisting of the phenothiazin-3-ones such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzene carboximidamides such as BIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, irlukast (CGP 45715A), and BAY x 7195.

45 [0058] The present invention still further relates to the combination of a compound of the invention together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

50 [0059] The present invention still further relates to the combination of a compound of the invention together with a antihistaminic H₁ receptor antagonists including cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

[0060] The present invention still further relates to the combination of a compound of the invention together with a gastroprotective H₂ receptor antagonist.

55 [0061] The present invention still further relates to the combination of a compound of the invention together with an α_1 - and α_2 -adrenoceptor agonist vasoconstrictor sympathomimetic agent, including propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

[0062] The present invention still further relates to the combination of a compound of the invention together with anticholinergic agents including ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine.

[0063] The present invention still further relates to the combination of a compound of the invention together with a β_1 - to β_4 -adrenoceptor agonists including metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol; or methylxanthanines including theophylline and aminophylline; sodium cromoglycate; or muscarinic receptor (M1, M2, and M3) antagonist.

[0064] The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

[0065] The present invention still further relates to the combination of a compound of the invention together with an inhaled glucocorticoid with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate.

[0066] The present invention still further relates to the combination of a compound of the invention together with (a) tryptase inhibitors; (b) platelet activating factor (PAF) antagonists; (c) interleukin converting enzyme (ICE) inhibitors; (d) IMPDH inhibitors; (e) adhesion molecule inhibitors including VLA-4 antagonists; (f) cathepsins; (g) MAP kinase inhibitors; (h) glucose-6 phosphate dehydrogenase inhibitors; (i) kinin-B₁ - and B₂ -receptor antagonists; (j) anti-gout agents, e.g., colchicine; (k) xanthine oxidase inhibitors, e.g., allopurinol; (l) uricosuric agents, e.g., probenecid, sulfapyrazone, and benzbromarone; (m) growth hormone secretagogues; (n) transforming growth factor (TGF β); (o) platelet-derived growth factor (PDGF); (p) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (q) granulocyte macrophage colony stimulating factor (GM-CSF); (r) capsaicin cream; (s) Tachykinin NK₁ and NK₂ receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; and (t) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892.

[0067] The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11).

[0068] The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

[0069] The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and farnesyl transferase inhibitors, VegF inhibitors, COX-2 inhibitors and antimetabolites such as methotrexate antineoplastic agents, especially antimitotic drugs including the vinca alkaloids such as vinblastine and vincristine;.

[0070] The compounds of the invention may also be used in combination with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antiseptic compounds such as Valant.

[0071] The compounds of the present invention may also be used in combination with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, ACE inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

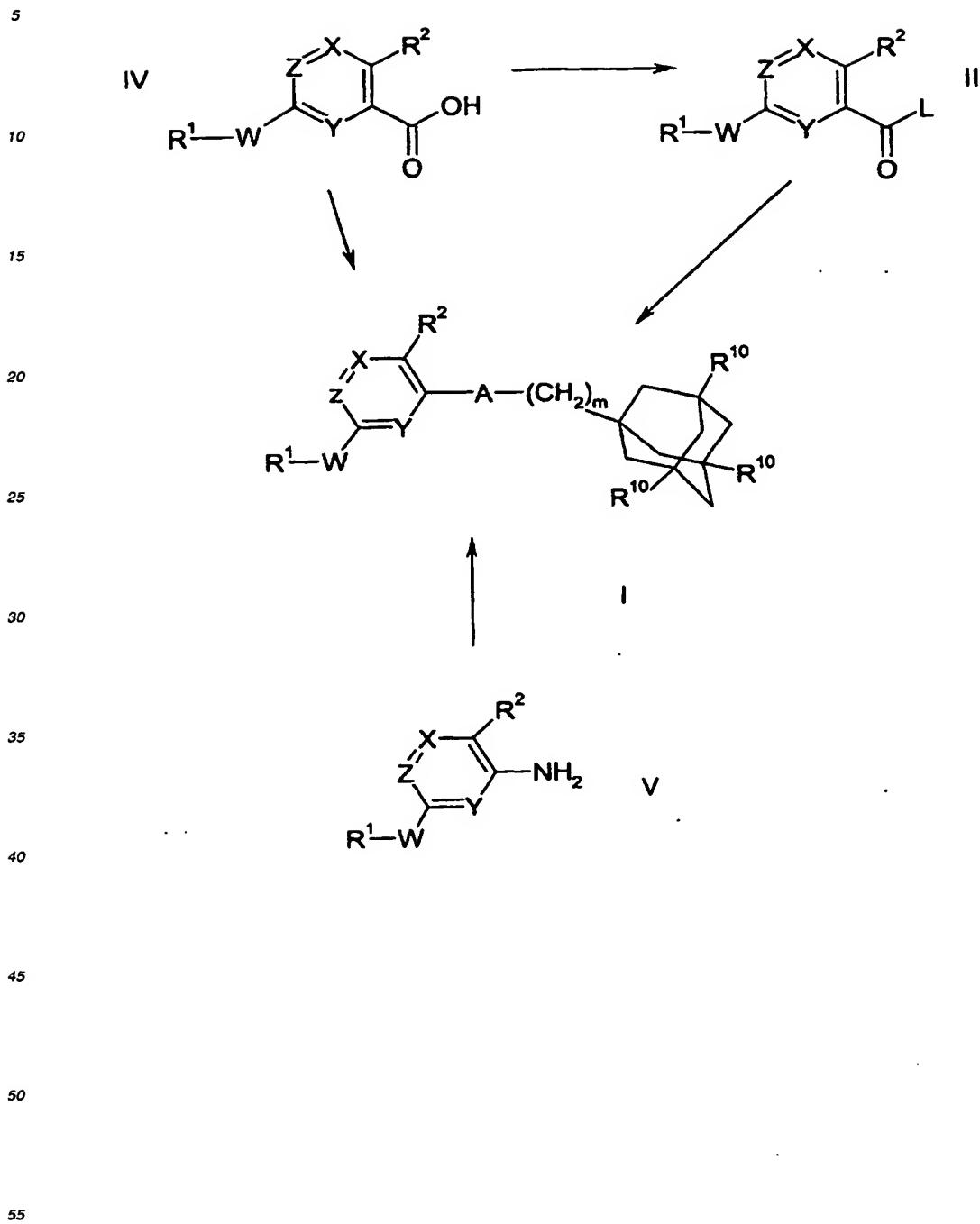
[0072] The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegiline and rasagiline, COMT inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

[0073] The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506, rapamycin, cyclosporine, azathioprine, and methotrexate;.

50

Detailed Description of the Invention

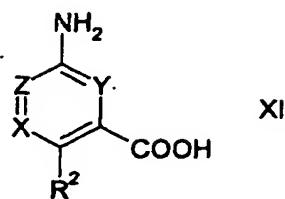
[0074] Compounds of the formula I may be prepared according to the following reaction schemes and discussion. Unless otherwise indicated A, X, Y, Z, W, m, n, o, p, q, r, and R¹ through R¹⁰ and structural formula I in the reaction schemes and discussion that follow are as defined above.

Scheme 1

Scheme 2

5

10

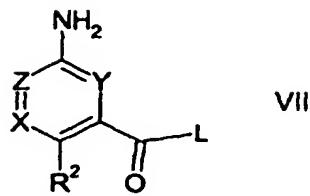


15

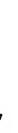


20

25

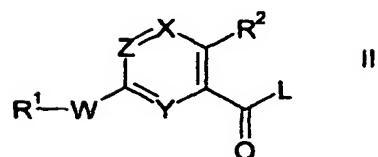


30



35

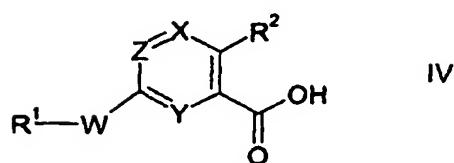
40



45



50



55

Scheme 3

5

10

15

20

25

30

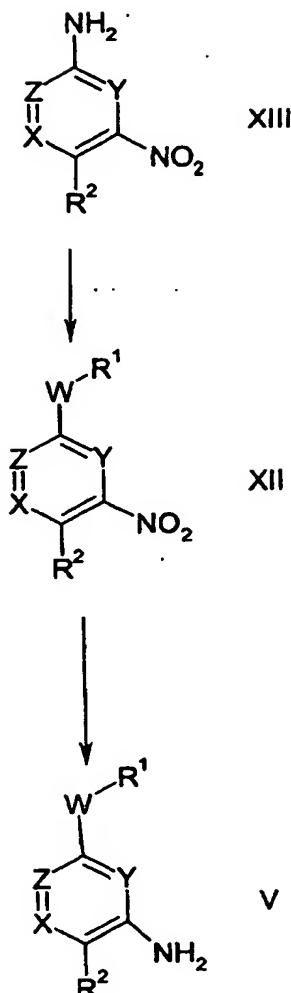
35

40

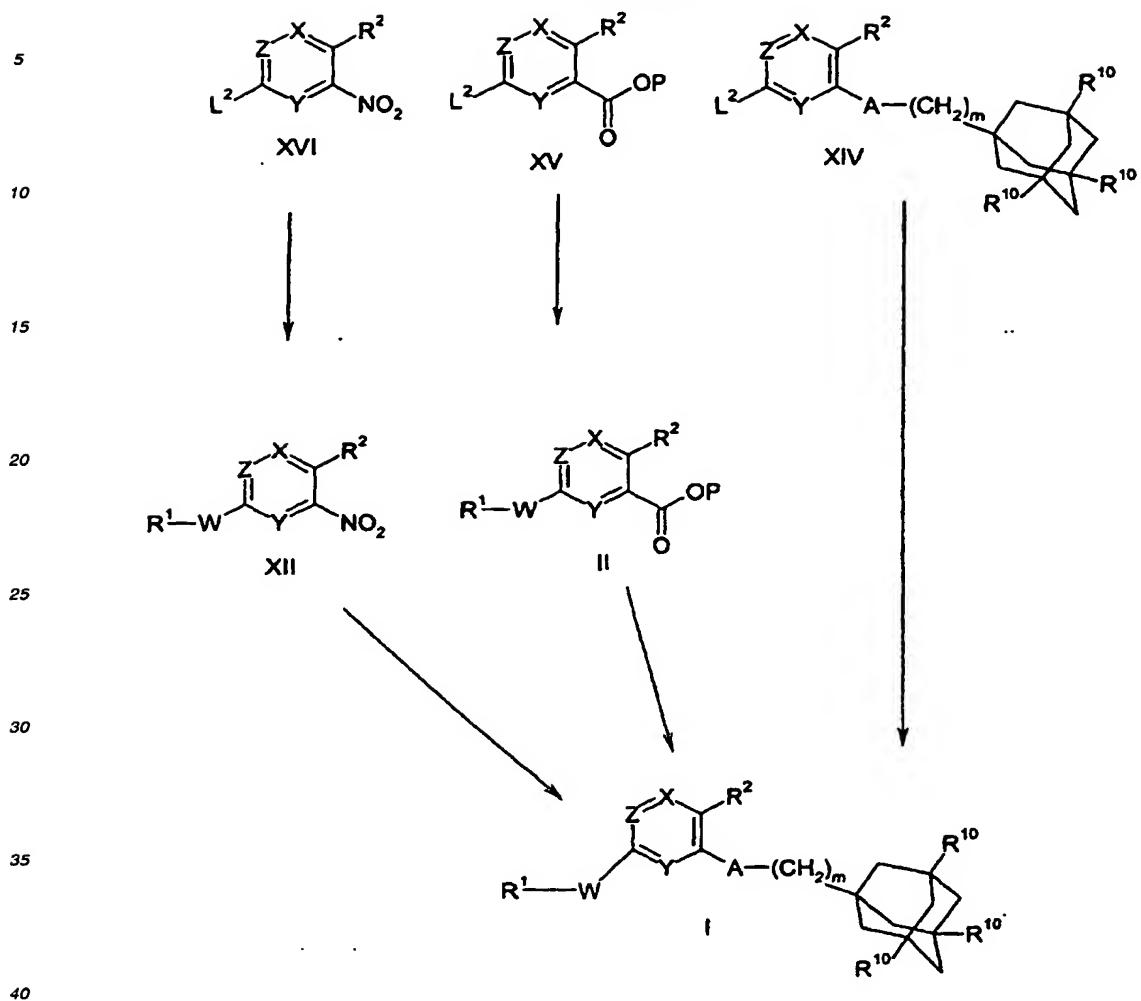
45

50

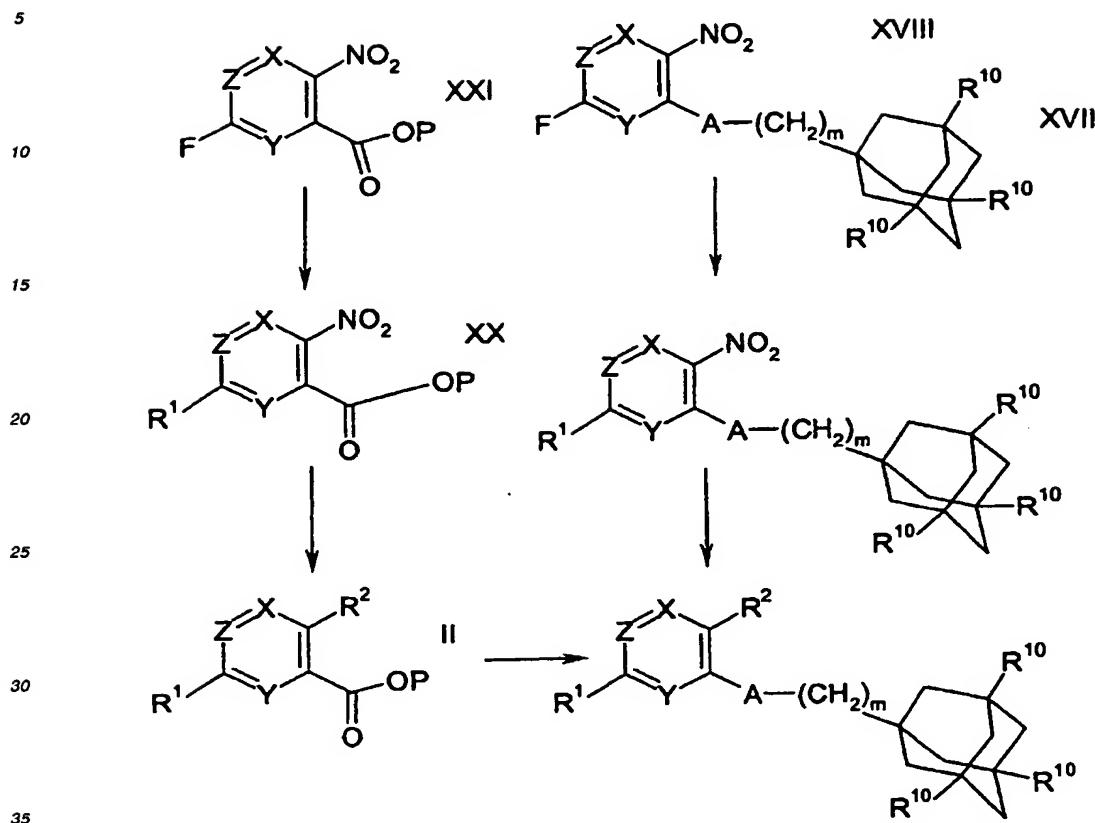
55



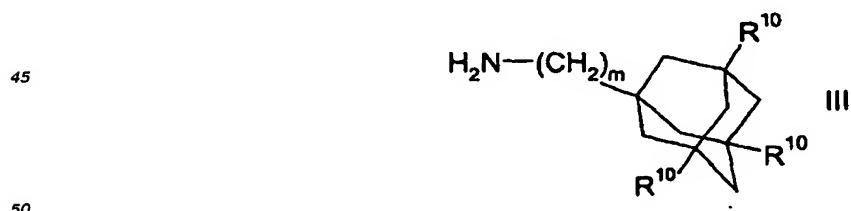
Scheme 4



Scheme 5



[0075] Scheme 1 refers to the preparation of compounds of formula I. Compounds of formula I, wherein A is -(C=O)-NH-, can be prepared from compounds of formula II, wherein L is a halo or an anhydride leaving group of the formula R-(C=O)-O- wherein R is optionally substituted alkyl or aryl, by reaction with a compound of formula III

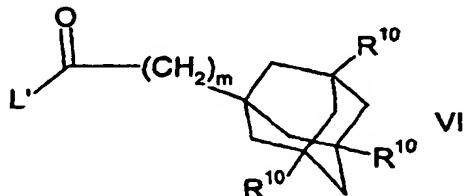


in the presence of a base. Suitable bases include an excess of compound of formula III as well as triethylamine, dimethylaminopyridine, sodium carbonate, pyridine, and Hünig's base, preferably triethylamine. The aforesaid reaction may be performed neat or in the presence of a solvent. Suitable solvents include methylene chloride, tetrahydrofuran, and toluene, preferably methylene chloride.

[0076] Alternatively, compounds of formula I, wherein A is -C=ONH-, can be prepared from compounds of formula IV, by reaction with a compound of formula III in the presence of a coupling reagent, such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) or dicyclohexyl carbodiimide (DCC) and hydroxybenzotriazole hydrate (HOBT), and

a base, such as diisopropylethylamine (DIEA) or triethylamine, in an aprotic solvent, such as methylene chloride. Suitable solvents include methylene chloride and dimethyl formamide, preferably methylene chloride. The aforesaid reaction may be run at a temperature from about 0°C to about 50°C, for a period from about 1 hour to about 16 hours (as illustrated in Comprehensive Organic Transformation, R.C. Larock, VCH Publisher, Inc. (1989) pp. 972-976).

5 [0077] Compounds of formula I, wherein A is -NH-(C=O)-, may be prepared from compounds of formula V by reaction with a compound of the formula VI



20 wherein L' is a leaving group such as chloro, fluoro, bromo, or an anhydride leaving group of the formula R-(C=O)-O-, wherein R is optionally substituted alkyl or aryl. The aforesaid reaction may be conducted in the presence of a suitable base. Suitable bases include an excess of compound of formula V as well as triethylamine, dimethylaminopyridine, sodium carbonate, pyridine, and Hünigs base, preferably triethylamine. The aforesaid reaction may be performed neat or in the presence of a solvent at a temperature from about 0°C to about 50°C, for a period from about 10 minutes to about 16 hours. Suitable solvents include methylene chloride, tetrahydrofuran, and toluene, preferably methylene chloride.

25 [0078] Compounds of formula II and IV can be made according to the methods of Scheme 2.

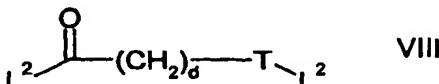
[0079] Compounds of formula V can be made according to the methods of Scheme 3.

30 [0080] Scheme 2 refers to the preparation of compounds of formulae IV and II, wherein L is a leaving group, W is a bond, >NR⁷, -(CH₂)_oNR⁷-, -O(CH₂)_pNR⁷-, -CONR⁷- or -SO₂NR⁷-; and R¹ is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring. Compounds of formulae II and IV can be converted into compounds of formula I according to the methods of Scheme 1.

35 [0081] Referring to Scheme 2, a compound of the formula IV, wherein W is a bond, >NR⁷, -(CH₂)_oNR⁷-, -O(CH₂)_pNR⁷-, -CONR⁷- or -SO₂NR⁷-; can be prepared from a compound of the formula II, wherein L is a leaving group such as a methoxy or ethoxy, by reaction with a saponification reagent such as with an aqueous base, such as sodium hydroxide in an alcoholic solvent such as methanol, ethanol or tert.-butanol. The aforesaid reaction may be run at a

40 temperature from about 0°C to about 100°C, for a period from about 1 hour to about 24 hours. When L is a leaving group such as tert.-butyl ester, a compound of the formula IV can be prepared by the reaction of a compound of a compound of formula II with an acid such as hydrochloric acid in a solvent such as dioxane at a temperature between 25°C to about 80°C, for a period from about 10 minutes to about 6 hours.

[0082] A compound of the formula II, wherein L is a leaving group such as alkoxy, W is a bond and R¹ is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, can be prepared from a compound of the formula VII by reaction with a compound of the formula

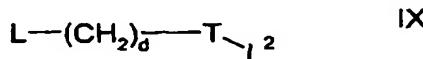


50 wherein d is 2 to 8 and wherein any of said -CH₂- groups may be optionally substituted by one or two R⁹ substituents, and wherein at least two of said -CH₂- groups are replaced with -NR¹⁰- (up to five -NR¹⁰-) and may optionally additionally contain 0-3 heteroatoms independently selected from the group consisting of -O- and -S(O)_n-, wherein n is an integer from zero to 2; or any single bond between any two CH₂ groups may optionally be a double bond; T is >C=O or >SO₂; wherein any carbon atom of said -(CH₂)_d- may optionally contain an oxo group and each L² is independently hydrogen, (C₁-C₆)alkyl or halo; under reductive amination conditions. The reductive amination is typically carried out with a reducing agent, such as sodium cyanoborohydride or sodium triacetoxyborohydride, preferably at a pH of between 6 and 8. The reaction is normally performed in a protic solvent, such as methanol or ethanol, or in a mixture of solvents, such as dichloroethane/methanol, at temperature of about -78°C to about 40°C for a period from about 1 hour to about 24 hours. (See A. Abdel-Magid, C. Maryanoff, K. Carson, Tetrahedron Lett., Vol. 34, Issue 31, 5595-98, 1990). Other

conditions involve the use of titanium isopropoxide and sodium cyanoborohydride (R.J.Mattson et al., *J.Org.Chem.*, 1990, 55, 2552-4) or involve the formation of the imine under dehydrating conditions followed by reduction (*Comprehensive Organic Transformation*, R.C. Larock, VCH Publisher, Inc (1989) pp. 421-425).

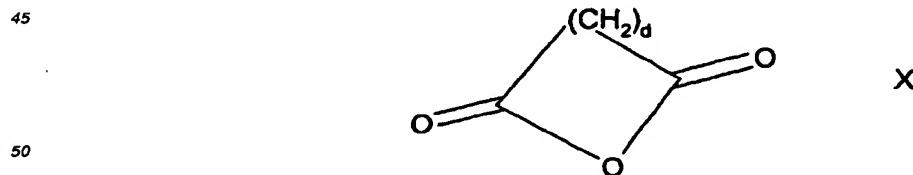
[0083] Alternatively, a compound of the formula II, wherein L is a leaving group such as alkoxy, and R¹ is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, can be prepared from the diazonium intermediate derived from a compound of the formula VII. The diazonium intermediate is prepared by reaction of a compound of the formula VII with an acid such as hydrochloric acid followed by treatment with sodium nitrite in a solvent such as glacial acetic acid at a temperature from about 0°C to about 30°C, and the reaction is generally run for a period of about 30 min to about 3 hours. The compound of the formula II is prepared by the reaction of the above diazonium intermediate with a compound of the formula VIII wherein wherein d is 2 to 8 and wherein any of said -CH₂- groups may be optionally substituted by one or two R⁹ substituents, and wherein at least two of said -CH₂- groups are replaced with -NR¹⁰- (up to five -NR¹⁰-) and may optionally additionally contain 0-3 heteroatoms independently selected from the group consisting of -O- and -S(O)_n-, wherein n is an integer from zero to 2; or any single bond between any two CH₂ groups may optionally be a double bond; T is >C=O or >SO₂; wherein any carbon atom of said -(CH₂)_d- may optionally contain an oxo group, and wherein any of said -CH₂- groups may optionally be replaced with either an oxo group or a heteroatom selected from -O- or -S(O)_n-, wherein n is an integer from zero to 2; or any single bond between any two CH₂ groups may optionally be a double bond; T is >C=O or >SO₂; and each L² is independently alkoxy or halo; under basic conditions. The reaction is typically carried out with sodium acetate as base at a temperature from about 0°C to about 120°C, and the reaction is generally run for a period of about 1 hour to about 24 hours. (For example, see R. D. Carroll et al., *J. Med. Chem.*, 1983, 26, 96-100).

[0084] Alternatively, one skilled in the art will also appreciate that a compound of formula II wherein W is a bond and R¹ is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, can be prepared by standard synthetic methods from a compound of the formula VII, wherein L is a protecting group such as alkoxy, by reaction with a bidentate reagent wherein two different transformable groups exist, such as an alkylating and acylating group of the formula



wherein L is a leaving group such as halo, L² is hydrogen, (C₁-C₆)alkyl or halo; wherein d is 2 to 8 and wherein any of said -CH₂- groups may be optionally substituted by one or two R⁹ substituents, and wherein at least two of said -CH₂- groups are replaced with -NR¹⁰- (up to five -NR¹⁰-) and may optionally additionally contain 0-3 heteroatoms independently selected from the group consisting of -O- and -S(O)_n-, wherein n is an integer from zero to 2; or any single bond between any two CH₂ groups may optionally be a double bond; T is >C=O or >SO₂; wherein any carbon atom of said -(CH₂)_d- may optionally contain an oxo group; or any single bond between any two CH₂ groups may optionally be a double bond.

[0085] Alternatively, one skilled in the art will also appreciate that a compound of formula II wherein R¹ is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, wherein the bridgehead atom is nitrogen, can be prepared by standard synthetic methods from a compound of the formula VII, wherein L is a protecting group such as alkoxy, by reaction with an anhydride reagent of the formula



wherein d is 2 to 8 and wherein any of said -CH₂- groups may be optionally substituted by one or two R⁹ substituents, and wherein at least two of said -CH₂- groups are replaced with -NR¹⁰- (up to five -NR¹⁰-) and may optionally additionally contain 0-3 heteroatoms independently selected from the group consisting of -O- and -S(O)_n-, wherein n is an integer from zero to 2; or any single bond between any two CH₂ groups may optionally be a double bond; wherein any carbon atom of said -(CH₂)_d- may optionally contain an oxo group; or any single bond between any two CH₂ groups may optionally be a double bond.

[0086] Alternatively, one skilled in the art will also appreciate that a compound of formula II wherein W is $>NR^7$, $-(CH_2)_oNR^7$, $-O(CH_2)_pNR^7$, $-SO_2NR^7$ or $-CONR^7$; can be prepared by reaction of a compound of formula VII with a compound of the formula $R^1-W'-L$, wherein $W'-L$ is halogen, triflate, $-(CH_2)_o$ -halo, $-(CH_2)_o$ -Tosyl, $-O(CH_2)_p$ -halo, $-O(CH_2)_o$ -Tosyl, $-(CH_2)_o(C=O)H$, $-O(CH_2)_o(C=O)H$, $-SO_2Cl$, $-CO_2H$, $-(C=O)Cl$, or $-(C=O)H$; wherein R^7 is hydrogen.

5 Compounds of formula II wherein R^7 is other than hydrogen can be prepared from compounds of formula II wherein R^7 is hydrogen by using standard transformations or coupling methods such as alkylation, acylation, reductive amination or sulfonylation. Such methods are well known to those skilled in the art and are described in standard organic chemistry text books such as March, Advanced Organic Chemistry, 641-676 (John Wiley & Sons, Inc., Fourth Edition, 1992).

10 [0087] Compounds of the formula VII can be prepared from compounds of the formula XI by reaction with an alcohol of the formula ROH , wherein R is optionally substituted (C_1-C_4)alkyl or (C_6-C_{10})aryl, in the presence of an acid (a so called Fischer esterification) or a coupling reagent, such as 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) or dicyclohexyl carbodiimide (DCC) and hydroxybenzotriazole hydrate (HOBT), and a base, such as diisopropylethylamine (DIEA) or triethylamine, in an aprotic solvent, such as methylene chloride. Suitable solvents include methylene chloride 15 and dimethyl formamide, preferably methylene chloride. The aforesaid reaction may be run at a temperature from about $0^\circ C$ to about $50^\circ C$, for a period from about 1 hour to about 16 hours (as illustrated in Comprehensive Organic Transformation, R.C. Larock, VCH Publisher, Inc. (1989) pp. 972-976).

15 [0088] Compounds of the formulae VIII, IX, X and XI are commercially available or can be made by methods well known to those of ordinary skill in the art.

20 [0089] Scheme 3 refers to the preparation of the compounds of formula V which are intermediates useful in the preparation of compound of formula I, in Scheme 1. Referring to Scheme 3, a compound of formula V is prepared by reduction of a compound of the formula XII. Reduction may be effected with hydrogen gas (H_2), using catalysts such as palladium on carbon (Pd/C), palladium on barium sulfate (Pd/BaSO₄), platinum on carbon (Pt/C), or tris(triphenylphosphine) rhodium chloride (Wilkinson's catalyst), in an appropriate solvent such as methanol, ethanol, THF, dioxane 25 or ethyl acetate, at a pressure from about 1 to about 5 atmospheres and a temperature from about $10^\circ C$ to about $60^\circ C$, as described in Catalytic Hydrogenation in Organic Synthesis, Paul Rylander, Academic Press Inc., San Diego, 31-63 (1979). The following conditions are preferred: Pd on carbon, methanol at $25^\circ C$ and 344.7 kPa (50 psi) of hydrogen gas pressure.

30 [0090] An alternative procedure employing the use of reagents such as ammonium formate and Pd/C in methanol at the reflux temperature under an inert atmosphere (e.g., nitrogen or argon gas) is also effective.

35 [0091] Another alternative reduction procedure, for use when R^1 contains a group incompatible with the above hydrogenation conditions (e.g., an olefin or halide group), is a dissolving metal reduction wherein the compound of formula XII is treated with a metal, such as zinc, tin or iron, in the presence of an acid such as hydrochloric or sulfuric acid. The aforesaid reaction may be run at a temperature from about $0^\circ C$ to about $100^\circ C$, for a period from about 1 hour to about 16 hours.

40 [0092] Compounds of the formula XII can be prepared from compounds of formula XIII by reaction with reagents of the formulae VIII, IX and X as described previously in Scheme 2 for the conversion of a compound of formula VII to II.

[0093] The starting materials of the formula XIII are either commercially available or known in the art.

45 [0094] Scheme 4 refers to alternate preparations of compounds of formula I.

40 [0095] Referring to Scheme 4, compounds of the formula I, wherein R^1 is a 5 to 10 membered saturated, unsaturated or partially unsaturated heterocyclic ring, can be prepared by an aryl palladium coupling reaction. Aryl palladium coupling reactions are well known to those skilled in the art. One well known coupling method, so called Buchwald and Hartwig conditions, involves the coupling of a compound of formula XIV, wherein L^2 is Cl, Br, I or triflate (TfO), with a compound of the formula R^1-H , wherein H is a hydrogen on a nitrogen ring atom, in the presence of a palladium (0) catalyst and a base. Palladium (0) catalysts include tris(dibenzylidene acetone)dipalladium(0) ($Pd_2(dba)_3$), di(dibenzylidene acetone) palladium(0) ($Pd(dba)_2$), palladium acetate ($Pd(OAc)_2$), and a suitable ligand, such as a triaryl phosphine ligand, tri(*t*-butyl)phosphine, 1,1'-bis(diphenylphosphanyl)ferrocene (DPPF), 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl (BINAP), or PHANEPHOS, preferably tri(*ortho*-tolyl)phosphine. Suitable bases include K_2CO_3 , K_2PO_4 , $CsCO_3$, $LiN(TMS)_2$ or an alkoxide base such as sodium methoxide, sodium ethoxide, potassium *t*-butoxide, preferably sodium *tert*-butoxide. Suitable solvents include toluene or an ethereal solvent, preferably dioxane. The aforesaid reaction may be run at a temperature of about $40^\circ C$ to $110^\circ C$ for about 1 to 48 hours. Such conditions are reviewed in Angew. Chem. Int. Ed. Engl., 1998, 37, 2046-2067 and are well known to those of ordinary skill in the art. Preferred Buchwald conditions use palladium acetate ($Pd(OAc)_2$) or palladium tetra-triphenylphosphine ($Pd(PPh_3)_4$) as the source of the palladium. Suitable solvents include THF, toluene or ethereal solvents. The aforesaid reaction may be run at a temperature of about $25^\circ C$ to $110^\circ C$ for about 1 to 4 hours, preferably 2 hours. Nickel catalysts, such as Ni (cod) (nickel 1,5-cyclooctadiene), are also well known.

55 [0096] Alternatively, compounds of formula I, can be prepared according to a so called Ullmann reaction by reaction of a compound of the formula XIV, wherein L^2 is a halide, with a compound of the formula R^1-H , wherein H is a hydrogen

on a nitrogen ring atom, in the presence of a suitable base and a suitable catalyst. Suitable bases include alkali metal carbonates or hydroxide bases, preferably potassium carbonate. Suitable catalysts include copper (0) catalyst, preferably finely powdered copper bronze. Suitable solvents for the aforesaid reaction include neat or polar aprotic solvents, such as dimethylformamide (DMF), N,N dimethylacetamide or N-methylpyrrolidinone (NMP). The aforesaid reaction

5 may be run at a temperature between about 80°C and 180°C for about 6 to 24 hours.

[0097] Alternatively, compounds of formula I, can be prepared according to a so called Stille coupling by reaction of a compound of the formula XIV, wherein L² is a halide or triflate, with a compound of the formula R¹-W-SnR₃, wherein R is a alkyl and W is a bond, -(CH₂)₆- , -(CH=CH)-, -C≡C-, -O(CH₂)₆- , -O(CH₂)_qO(CH₂)_r- , -(CH₂)_rO(CH₂)_r- , -NR⁷(CH₂)₆- , -(CH₂)_rNR⁷(CH₂)_r- , -O(CH₂)_qNR⁷(CH₂)_r- , -NR⁷(CH₂)_qO(CH₂)_r- , and -S(O)_nCH₂-; in the presence of a suitable base and a suitable catalyst. If necessary, a salt such as lithium chloride, ammonium hydroxide, copper(I) bromide, may be used. Suitable bases include alkali metal carbonate or hydroxide base, preferably potassium carbonate. Suitable catalysts include palladium acetate (Pd(OAc)₂), tetrakis(triphenylphosphine)palladium (Pd(PPh₃)₄) and dichlorobis(triphenylphosphine)palladium. Suitable solvents for the aforesaid reaction include neat or polar aprotic solvents, such as dimethylformamide (DMF), tetrahydrofuran, 1,4-dioxane, benzene, toluene, dimethoxyethane, or N-methylpyrrolidinone (NMP), preferably tetrahydrofuran and 1,4-dioxane. The aforesaid reaction may be run at a temperature between about 20 to 160°C, usually 20 to 130 °C for about 10 minutes to 5 days, usually 30 minutes to 15 hours. (See Stille, J.K., Angew. Chem. Int. Ed. Eng., 1986, 25, 508-524).

[0098] Alternatively, compounds of formula I, can be prepared according to a so called Stille coupling by reaction of a compound of the formula XIV, wherein L² is SnR₃, wherein R is a alkyl, with a compound of the formula R¹-W' wherein W' is a halide, triflate, -(C=O)H, -(C=O)R⁶, -(C=O)-Cl, -CH=CH-(halide), -O(CH₂)_q-O-(CH₂)_r-(halide), or -(CH₂)_rO(CH₂)_r-(halide); according to methods to those described above for the Stille coupling.

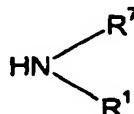
[0099] Alternatively, compounds of formula I, can be prepared according to a so called Negishi coupling by reaction of a compound of the formula XIV, wherein L² is a halide or triflate, with a compound of the formula R¹-W-zinc halide. The catalyst may be selected from those typically employed for the so-called reaction (for example, tetrakis(triphenylphosphine)palladium, tetrakis(triphenylphosphine)nickel, dichlorobis(triphenylphosphine)palladium, dichlorobis(triphenylphosphine)palladium, / n-BuLi, dichlorobis(1,1-bis(diphenylphosphino)ferrocene)palladium and dichlorobis(1,4-bis(diphenylphosphino)butane)palladium). Suitable solvents include tetrahydrofuran, diethylether and dimethoxyethane, preferably tetrahydrofuran. The reaction is carried out at a temperature in the range from 20 to 160 °C, usually 20 to 130 °C for 10 minutes to 5 days, usually 30 minutes to 15 hours. Alternatively, one skilled in the art will appreciate that the reactive groups of the reagents can be reversed. Thus, one skilled in the art will appreciate that L² in the aforesaid reaction can be the zinc halide coupled to an R¹W'-halide or triflate. (Knochel, P. And Singer, R.D. Chem. Rev., 1993, 93, 2117-2188).

[0100] Alternatively, coupling can be carried out by a so called Suzuki coupling reaction of said compound of formula XIV, wherein L² is I, Br, Cl, or triflate, with an R¹-W-borate or R¹-W-boronic acid, a catalyst, a base and a dehydrating agent. Suitable borates include (HO)₂B-, 9-BBN, and alkylboranes. Suitable catalysts include copper or palladium, preferably copper (II) acetate or palladium acetate (Pd(OAc)₂), palladium triphenylphosphine or Pd(dppf)Cl₂. Suitable dehydrating agents include 4 angstrom molecular sieves. Suitable bases include tertiary amine bases, such as triethylamine or pyridine, Na₂CO₃, sodium ethoxide, and K₃PO₄. Suitable solvents include methylene chloride, dimethyl sulfoxide (DMSO) or tetrahydrofuran (THF). The aforesaid reaction is typically performed under an atmosphere of oxygen

40 gas at a temperature of about 10°C to 50°C, preferably about 23°C for about 6 to 72 hours. Palladium-catalyzed boronic acid couplings are described in Miyaura, N., Yanagi, T., Suzuki, A. Syn. Comm. 1981, 11, 7, p. 513.

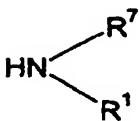
[0101] Alternatively, the Suzuki coupling may be carried out in cases where L² is B(OH)₂ and R¹-W is substituted with I, Br, Cl, or triflate or H wherein H is a hydrogen on a nitrogen atom, using a copper or palladium catalyst, preferably copper (II) acetate or palladium acetate using methods analogous to those of the preceding paragraph.

[0102] Compounds of formula I wherein W is -Nk⁷-(C=O)- can be prepared from compounds of formula XIV, wherein L² is -CO₂H or -(C=O)-Cl, by reaction with a reagent of the formula



55 according to standard methods well known to those skilled in the art.

[0103] Compounds of formula I wherein W is -NR⁷SO₂- can be prepared from compounds of formula XIV, wherein L² is -SO₂-Cl, by reaction with a reagent of the formula



according to standard methods well known to those skilled in the art.

[0104] Alternatively, compounds of formula I can also be prepared from compounds of formula XV or XVI via intermediates of the formula II and XII. The intermediates of the formula II and XII can be converted to compounds of formula I according to the methods of Schemes 1 and 3 respectively. The compounds of formulae II and XII can be prepared from compounds of the formulae XV and XVI, respectively, by coupling reactions analogous to those described above for the conversion of compounds of formula XIV to formula I.

[0105] Compounds of the formula XV and XVI are commercially available or can be made by methods well known to those skilled in the art.

[0106] Scheme 5 refers to an alternate preparation of compounds of formula I. Referring to Scheme 5, a compound of formula I is prepared from a compound of formula XVII by reduction with tin in the presence of an acid such as hydrochloric acid followed by a so called Sandmeyer reaction wherein a diazonium intermediate is prepared by treatment with sodium nitrite followed by a quench with a cuprous halide such as cuprous chloride or cuprous bromide.

20 Suitable solvents include alcohols such as methanol and ethanol. The aforesaid reaction is conducted at a temperature from about -20°C to about 0°C, and the reaction is generally run for a period of about 1 to 48 hours.

[0107] The compound of formula XVII, wherein R¹-W- is a standard transformable group, such as R¹-O-, R¹-(CH₂)_oO-, R¹-O(CH₂)_pO-, R¹-(CH₂)_rO(CH₂)_qO-, R¹-(NR⁷)-, R¹-(CH₂)_oNR⁷-, R¹-O(CH₂)_pNR⁷-, R¹-(CH₂)_rNR⁷-(CH₂)_qO-, R¹-NR⁷(CH₂)_qO-, R¹-CONR⁷-, R¹-S-, R¹-CH₂S-; or W is a bond and R¹ is a 5 to 10 membered saturated, 25 unsaturated or partially unsaturated heterocyclic ring containing an NH can be prepared from a compound of the formula XVIII by reaction with a nucleophile according to standard chemical methods well known to those skilled in the art. Methods for nucleophilic aromatic substitution are reviewed in Belfield *et al.*, *Tetrahedron*, 55, 11399-11428 (1999), in March, *Advanced Organic Chemistry*, 641-676 (John Wiley & Sons, Inc., Fourth Edition, 1992).

[0108] Compounds of formula XVIII are commercially available or can be made by methods known to those skilled in the art.

[0109] Alternatively, compounds of formula I and II can be prepared from compounds of formula XX by analogous Sandmeyer methods as described above.

[0110] Compounds of formula XX can be prepared from compounds of formula XXI by methods analogous to the conversion of compounds of formula XVIII to XVII described above.

35 [0111] Compounds of formula XXI are commercially available or can be made by methods well known to those skilled in the art.

[0112] The compounds of the formula I which are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate a compound of the formula I from the reaction mixture 40 as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent, and subsequently convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt 45 is obtained.

[0113] The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as chloride, bromide, iodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, 50 methanesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

[0114] Those compounds of the formula I which are also acidic in nature, e.g., where R⁴ includes a 6-azauracil or barbituric acid moiety, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline-earth metal salts and particularly, the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare 55 the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the herein described acidic compounds of formula I. These non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium and magnesium, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable

cations, and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum product yields.

[0115] The activity of the compounds of the invention for the various disorders described above can be determined according to one or more of the following assays. All of the compounds of the invention, that were tested, had an IC_{50} of less than 1 μ M in the *in vitro* human monocyte assay described below.

10 PHARMACOLOGICAL ANALYSIS

[0116] Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the P2X₇ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37 (3), p. 126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. Alternatively, the propidium dye YOPRO-1 can be substituted for ethidium bromide so as to detect uptake of the dye. The increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound on the P2X₇ receptor.

[0117] In this manner, the compounds of the invention can be tested for antagonist activity at the P2X₇ receptor. 96-Well flat bottomed microtitre plates are filled with 250 μ l of test solution comprising 200 μ l of a suspension of THP-1 cells (2.5×10^6 cells/ml, more preferably prestimulated as described in the literature with a combination of LPS and TNF to promote receptor expression) containing 10^{-4} M ethidium bromide, 25 μ l of a high potassium, low sodium buffer solution (10mM Hepes, 150 mM KCl, 5 mM D-glucose and 1.0% FBS at pH 7.5) containing 10^{-5} M bbATP, and 25 μ l of the high potassium buffer solution containing 3×10^{-5} M test compound (more preferably 5×10^{-4} M, more preferably 1×10^{-4} M, more preferably 1×10^{-3} M). The plate is covered with a plastic sheet and incubated at 37°C for one hour. The plate is then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) can be used separately in the test as controls. From the readings obtained, a pIC_{50} figure can be calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%.

[0118] In like manner, the compounds of the invention can be tested for antagonist activity at the P2X₇ receptor using the cytokine IL-1 β as the readout. Blood collected from normal volunteers in the presence of heparin is fractionated using lymphocyte separation medium obtained from Organon Technica (Westchester, PA). The region of the resulting gradient containing banded mononuclear cells is harvested, diluted with 10 ml of Maintenance Medium (RPMI 1640, 5% FBS, 25 mM Hepes, pH 7.2, 1% penicillin/streptomycin), and cells are collected by centrifugation. The resulting cell pellet was suspended in 10 ml of Maintenance Medium and a cell count was performed. In an average experiment, 2×10^5 mononuclear cells are seeded into each well of 96-well plates in a total volume of 0.1 ml. Monocytes are allowed to adhere for 2 hours, after which the supernatants are discarded and the attached cells are rinsed twice and then incubated in Maintenance Medium overnight at 37°C in a 5% CO₂ environment.

[0119] The cultured monocytes can be activated with 10 ng/ml LPS (E. coli serotype 055:B5; Sigma Chemicals, St. Louis, MO). Following a 2-hour incubation, the activation medium is removed, the cells are rinsed twice with 0.1 ml of Chase Medium (RPMI 1640, 1% FBS, 20 mM Hepes, 5 mM NaHCO₃, pH 6.9), and then 0.1 ml of Chase Medium containing a test agent is added and the plate is incubated for 30 minutes; each test agent concentration can be evaluated in triplicate wells. ATP then is introduced (from a 100 mM stock solution, pH 7) to achieve a final concentration of 2 mM and the plate is incubated at 37°C for an additional 3 hours. Media were harvested and clarified by centrifugation, and their IL-1 β content was determined by ELISA (R&D Systems; Minneapolis, MN).

[0120] The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous), topical or rectal administration or in a form suitable for administration by inhalation or insufflation.

[0121] For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable ad-

ditives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g., lecithin or acacia); non-aqueous vehicles (e.g., almond oil, oily esters or ethyl alcohol); and preservatives (e.g., methyl or propyl p-hydroxybenzoates or sorbic acid).

5 [0122] For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

[0123] The compounds of formula I can also be formulated for sustained delivery according to methods well known to those of ordinary skill in the art. Examples of such formulations can be found in United States Patents 3,538,214, 4,060,598, 4,173,626, 3,119,742, and 3,492,397, which are herein incorporated by reference in their entirety.

10 [0124] The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

15 [0125] The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

[0126] For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution, dry powder formulation or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, 20 with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, heptafluoroalkanes, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable 25 powder base such as lactose or starch.

[0127] A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above (inflammation) is 0.1 to 200 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

30 [0128] The compound of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99% w (per cent by weight), more preferably from 0.10 to 70% w, of active ingredient, and, from 1 to 99.95% w, more 35 preferably from 30 to 99.90% w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

[0129] Aerosol formulations for treatment of the conditions referred to above in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains 20 μ g to 1000 μ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μ g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

40 [0130] Aerosol combination formulations for treatment of the conditions referred to above (e.g., adult respiratory distress syndrome) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 1 μ g to 1000 μ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μ g to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

45 [0131] Aerosol formulations for treatment of the conditions referred to above (e.g., adult respiratory distress syndrome) in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains from about 20 μ g to 1000 μ g of the compound of the invention. The overall daily dose with an aerosol will be within the range 100 μ g to 10 mg of the p38 kinase inhibitor. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

50 [0132] The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million (d) and are referenced to the deuterium lock signal from the sample solvent (deuteriochloroform unless otherwise specified). Mass Spectral data were obtained using a Micromass ZMD APCI Mass Spectrometer equipped with a Gilson gradient high performance liquid chromatograph. The following solvents and gradients were used for the analysis. Solvent A; 98% water/2% acetonitrile/0.01% formic acid and solvent B; acetonitrile containing 0.005% formic acid. Typically, a gradient was run over a period of about 4 minutes starting at 95% solvent A and ending with 100% solvent B. The mass spectrum of the major eluting component was then obtained in positive or negative ion mode scanning a molecular weight range from 165 AMU to 1100 AMU. Specific rotations were measured at room temperature using the sodium D line (589 nm). Commercial reagents were utilized

without further purification. THF refers to tetrahydrofuran. DMF refers to N,N-dimethylformamide. Chromatography refers to column chromatography performed using 32-63 mm silica gel and executed under nitrogen pressure (flash chromatography) conditions. Room or ambient temperature refers to 20-25°C. All non-aqueous reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Concentration at reduced pressure means that a rotary evaporator was used.

[0133] One of ordinary skill in the art will appreciate that in some cases protecting groups may be required during preparation. After the target molecule is made, the protecting group can be removed by methods well known to those of ordinary skill in the art, such as described in Greene and Wuts, "Protective Groups in Organic Synthesis" (2nd Ed, John Wiley & Sons 1991).

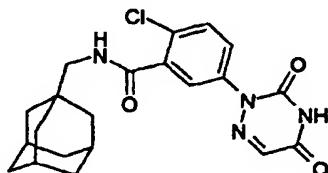
10

EXAMPLE 1

N-ADAMANTAN-1-YLMETHYL-2-CHLORO-5-(3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]TRIAZIN-2-YL)-BENZAMIDE

15

[0134]

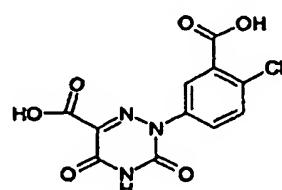


25

A: 2-(3-Carboxy-4-chloro-phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]triazine-6-carboxylic acid

30

[0135]



40

[0136] To a mechanically stirred solution of 5-amino-2-chloro-benzoic acid methyl ester (5.0 g, 26.9 mmol) in glacial acetic acid (100 ml) was added 12 N hydrochloric acid (7.5 ml). After 30 minutes at room temperature the reaction mixture was cooled to 10°C and a solution of NaNO₂ in water (5 ml) was added dropwise at a rate that kept the reaction temperature between 10° and 15°C. During this time it was observed that the reaction went from purple to light brown. After stirring for 30 minutes at 10°C sodium acetate (5.4 g) followed by (3-ethoxycarbonylamino-3-oxo-propionyl)-carbamic acid ethyl ester (7.2 g) were added at once. After stirring for 20 minutes at 10°C followed by 1 hour at room temperature an additional 2.2 g of sodium acetate was added. After stirring at reflux for 6 hours the reaction mixture was cooled to room temperature and 50% aqueous sulfuric acid (29 ml) was added. After stirring the resulting mixture at reflux for 2 hours the mixture was cooled to room temperature, diluted with water (135 ml) and filtered. The precipitate was washed with water and dried under vacuum. The crude solid was recrystallized from isopropyl ether to give 3.8 g (46%) of the title intermediate as an orange solid. Mass spec [M-1] 3:1 ratio of 310.1 and 312.1; ¹H nmr (500 MHz, CD₃OD) δ 7.64 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 2.6 Hz, 1H).

50

55

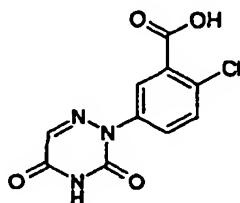
EP 1 310 493 B1

B: 2-Chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid

[0137]

5

10



15 [0138] A suspension of 2-(3-carboxy-4-chloro-phenyl)-3,5-dioxo-2,3,4,5-tetrahydro-[1,2,4]-triazine-6-carboxylic acid (3.4 g) in mercaptoacetic acid (2 ml) was stirred at 175°C. After 20 hours the resulting solution was cooled to room temperature during which time a precipitate formed. The mixture was dumped into ice-water, stirred for 30 minutes and filtered to give a yellow solid. The solid was dried under vacuum for 24 hours to give 2.1 g of the title intermediate. Mass spec [M-1] 3:1 ratio of 266.1 and 268.1; ¹H NMR (500 MHz, CD₃OD) δ 7.58 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.72 (dd, J = 2.6 and 8.8 Hz), 8.09 (d, J = 2.6 Hz).

20

C: N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide

25 [0139] To a stirred solution of 2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid (48 mg, 0.18 mmol), EDCI (67 mg) and HOBT (47 mg) in DMF (1.5 ml) was added a solution of 1-adamantane methylamine (36 mg) in DMF (0.5 ml). After 20 minutes triethylamine (49 μl) was added. After 18 hours the reaction mixture was diluted with dichloromethane (75 ml) and washed sequentially with water, 1N HCl and brine. The organic layer was dried over magnesium sulfate, filtered and concentrated under vacuum to give 73 mg of an amorphous solid. The solid was purified by silica gel chromatography eluting with 1:1 ethylacetate/hexanes to give 22 mg of the title compound, as a white amorphous solid. Mass spec [M-1] 3:1 ratio of 413.5 and 415.5; ¹H NMR (500 MHz, CD₃OD) δ 1.61 (s, 6H), 1.68 (d, J = 11.6 Hz, 3H), 1.75 (d, J = 12.5 Hz, 3H), 1.97 (s, 3H), 3.05 (s, 2H), 7.54 - 7.56 (m, 2H), 7.61 - 7.65 (m, 2H), 8.54 (broad t, 1H).

30 [0140] Examples 2-3 are presented in Table 1 and were prepared analogously to the synthesis outlined in Example 1C, coupling the appropriate amine to 2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid. Final products were analyzed by LC/MS using a Micromass ZMD LC/MS (ESI mode). The method used for the HPLC mobile phase gradient change was as follows:

40

Time (min)	A%	B%
0.00	95	5
1.0	80	20
2.3	50	50
3.7	0	100
3.7	95	5
Solvent A= 98% Water + 2% Acetonitrile + 0.01% Formic Acid		
Solvent B = Acetonitrile + 0.005% Formic Acid		

45

50

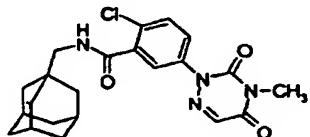
55

TABLE 1

Ex.	Structure	Mass Spectra (ES+)	Mass Spectra (ES-)	LC Retention Time (min)
2		452.0	450.0	2.4
3		—	427.3	2.8

EXAMPLE 4**N-ADAMANTAN-1-YLMETHYL-2-CHLORO-5-(4-METHYL-3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]TRIAZIN-2-YL)-BENZAMIDE**

[0141]



[0142] To a stirred solution of N-adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide (66 mg, 0.159 mmol) in dioxane (1.5 ml) was added methanol (0.32 ml) followed by a 2.0 M solution of (trimethylsilyl)diazomethane (0.32 ml). After stirring for 18 hours at ambient temperature the mixture was concentrated under reduced pressure to give 67 mg of a light yellow amorphous solid. Mass Spectrum (ES+) 429.6; (ES-) 427.6. Liquid chromatography retention time = 2.8 min (using the LC/MS and method outlined for the examples in Table 1).

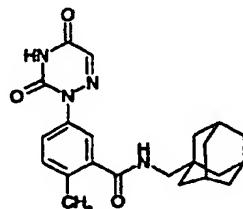
50

55

EXAMPLE 5**N-ADAMANTAN-1-YLMETHYL-5-(3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]TRIAZIN-2-YL)-2-METHYL-BENZAMIDE**

5 [0143]

10

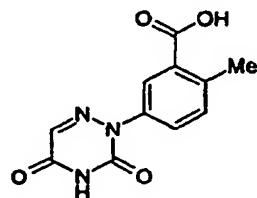


15

A: 2-Methyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid

20 [0144]

25



30 [0145] 5-Amino-2-chloro-benzoic acid methyl ester (3.5 g, 21.2 mmol) was dissolved in glacial acetic acid (80 ml) and 5.5 ml of concentrated HCl was added. After stirring with an overhead stirrer for 30 minutes at ambient temperature the mixture was cooled to 10°C and a solution of NaNO₂ (1.6 g) in water (4 ml) was added dropwise, keeping the internal temperature below 15°C. During this addition the reaction mixture changed from amber to a cloudy orange. After 30 minutes sodium acetate (3.8 g, 46.6 mmol) and (3-ethoxycarbonylamino-3-oxo-propyl)-carbamic acid ethyl ester (5.7 g, 23.3 mmol) were added at once. After 10 minutes the reaction was warmed to ambient temperature. After 1 hour additional sodium acetate (1.7 g, 21.2 mmol) was added and the reaction mixture was heated at reflux. After 3 hours the deep red-brown mixture was treated with 50% sulfuric acid (23 ml) and heated again at reflux. After 2 hours the mixture was concentrated under reduced pressure and then water (200 ml) was added. After stirring for 30 minutes the gold precipitate (3.5 g) was collected by filtration. The resulting solid was suspended in 3 ml of mercaptoacetic acid and stirred at 175°C. After 4 hours the mixture was allowed to cool and sit for 16 hours. The mixture was diluted with water (100 ml) and stirred for 1 hour. The resulting brown solid (2.1 g) was collected by filtration. Mass spectrum [M-1] 246.4.

45

B: N-[2-(2-Chloro-phenyl)-ethyl]-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-methyl-benzamide

50

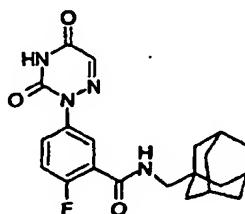
[0146] The title compound was prepared using the method outlined in **Example 1C**, coupling 2-methyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzoic acid with 1-adamantane methylamine. The product was a colorless oil. MS (ES+) 395.6; (ES-) 393.5; LC retention time = 2.5 min (using the LC/MS and method outlined for the examples in Table 1).

55

EXAMPLE 6**N-ADAMANTAN-1-YLMETHYL-5-(3,5-DIOXO-4,5-DIHYDRO-3H-[1,2,4]TRIAZIN-2-YL)-2-FLUORO-BENZAMIDE**

5 [0147]

10



15

[0148] The title compound was prepared using the method outlined in **Example 5**, starting with 5-amino-2-chlorobenzoic acid methyl ester. The product was a colorless oil. Mass Spectrum (ES+) 399.5; (ES-) 397.5. Liquid chromatography retention time = 2.6 minutes (using the LC/MS and method outlined for the examples in Table 1).

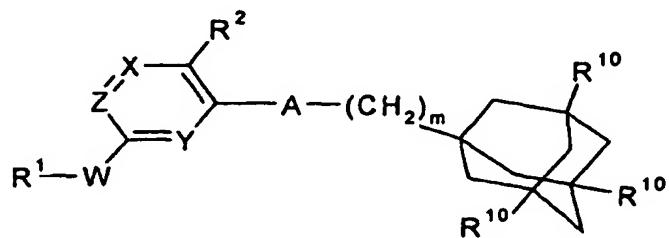
20

Claims

1. A compound of the formula

25

30



35

I

wherein A is -(C=O)NH- or -NH(C=O)-;

40 X, Y and Z are =(CR³)-, =(CR⁴)-, and =(CR⁵)-; or =N-, =(CR⁴)-, and =(CR⁵)-; or =(CR³)-, =N-, and =(CR⁵)-; or = (CR³)-, =(CR⁴)-, and =N-; or =N-, =(CR⁴)-, and =N-; or =(CR³)-, =N-, and =N-; or =N-, =N-, and CR⁵, respectively; W is a bond, -O-, >(C=O), -(CH₂)_o-, -(CH=CH)-, -C≡C-, -(CH₂)_oO-, -O(CH₂)_o-, -O(CH₂)_pO-, -O(CH₂)_qO(CH₂)_r-, -CR⁶(OH)-, -(CH₂)_oO(CH₂)_r-, -(CH₂)_oO(CH₂)_qO-, >NR⁷, -(CH₂)_oNR⁷-, -NR⁷(CH₂)_o-, -(CH₂)_rNR⁷(CH₂)_r-, -O(CH₂)_pNR⁷-, -O(CH₂)_qNR⁷(CH₂)_r-, -(CH₂)_rNR⁷(CH₂)_qO-, -NR⁷(CH₂)_qO-, -NR⁷(CH₂)_qO(CH₂)_r-, -CONR⁷-, -NR⁷CO-, >S(O)_n, -S(O)_nCH₂-, -CH₂S(O)_n-, -SO₂NR⁷-, or -NR⁷SO₂;

45 m is an integer from 1 to 2;

n is an integer from 0 to 2;

o is an integer from 1 to 6;

p is an integer from 2 to 6;

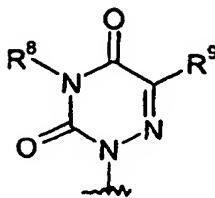
50

q is an integer from 2 to 3;

r is an integer from 1 to 3;

R¹ is the group

55



wherein R⁸ is selected from the group consisting of hydrogen, CF₃-, (C₁-C₆)alkyl, HO-(C₂-C₆)alkyl or (C₃-C₈)cycloalkyl group.

wherein R⁹ is selected from the group consisting of hydrogen, (C₁-C₆)alkyl, CF₃-CH₂-, HO-(C₂-C₆)alkyl or (C₃-C₈)cycloalkyl group.

15 R² is selected from the group consisting of (i) hydrogen, (ii) halogen, (iii) cyano, (iv) (C₁-C₄)alkyl optionally substituted by one to four chloro or fluoro, (v) (C₂-C₄)alkenyl; (vi) (C₂-C₄)alkynyl and (vii) (C₁-C₄)alkyloxy optionally substituted by one to four chloro or fluoro;

20 R³, R⁴ and R⁵ are each independently selected from the group consisting of (i) hydrogen; (ii) halogen, (iii) cyano, (iv) nitro, (v) amino, (vi) hydroxyl, (vii) (C₁-C₆)alkyl optionally substituted by one to four chloro or fluoro, (viii) (C₃-C₆)cycloalkyl optionally substituted by one to four chloro or fluoro, (ix) (C₁-C₆)alkyloxy optionally substituted by one to four chloro or fluoro, and (x) (C₃-C₈)cycloalkyloxy optionally substituted by one to four chloro or fluoro;

R⁶ is hydrogen or (C₁-C₆)alkyl;

R⁷ is hydrogen, (C₁-C₆)alkyl or (C₃-C₈)cycloalkyl;

25 each R¹⁰ is independently selected from the group consisting of hydrogen or halo; or a pharmaceutically acceptable salt or solvate thereof.

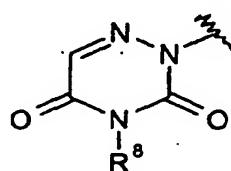
2. A compound according to claim 1 wherein X, Y and Z are =(CR³)-, =(CR⁴)-, and =(CR⁵)-; respectively.

30 3. A compound according to any of the previous claims wherein one of R³, R⁴ or R⁵ is selected from the group consisting of (i) hydrogen (ii) halogen, (iii) cyano, (iv) nitro, (v) amino, (vi) hydroxyl, (vii) (C₁-C₆)alkyl optionally substituted by one to four chloro or fluoro, (viii) (C₃-C₆)cycloalkyl optionally substituted by one to four chloro or fluoro, (ix) (C₁-C₆)alkyloxy optionally substituted by one to four chloro or fluoro.

35 4. A compound according to any of the previous claims wherein m is one.

5. A compound according to any of the previous claims wherein A is -(C=O)NH-.

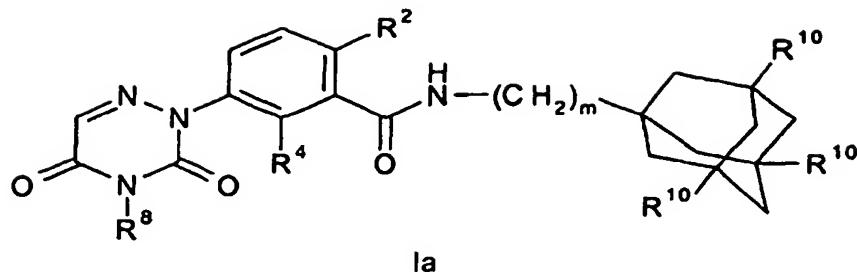
40 6. A compound according to claims 1 to 13 wherein R¹ is



50 7. A compound according to any of the previous claims wherein R⁸ is selected from the group consisting of hydrogen and (C₁-C₆)alkyl.

7. A compound according to any of the previous claims wherein W is a bond.

55 8. A compound according to claim 1 wherein said compound of formula I has the formula



wherein m is an integer from 1 to 2;

R² is fluoro or chloro;

15 R⁴ is selected from the group consisting of hydrogen, halogen, cyano, hydroxyl, (C₁-C₃)alkyl, (C₃-C₆)cycloalkyl,

(C₁-C₃)alkyloxy, -CF₃, -OCF₃ and (C₃-C₆)cycloalkyloxy;

R⁸ is a hydrogen atom or a (C₁-C₆)alkyl, CF₃-CH₂-, HO-(C₂-C₆)alkyl or (C₃-C₈)cycloalkyl group;

R¹⁰ is hydrogen or fluoro;

or a pharmaceutically acceptable salt or solvate thereof.

20

9. A compound selected from the group consisting of:

N-Adamantan-1-ylmethyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide;

N-Adamantan-1-ylmethyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-methyl benzamide;

25

N-Adamantan-1-ylmethyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-fluoro benzamide;

N-Adamantan-1-ylmethyl-2-chloro-5-(4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide;

2- Chloro-N-(3,5-difluoro-adamantan-1-ylmethyl)-5-(3,5-dioxo-4,5-dihydro-3H [1,2,4]triazin-2-yl)-benzamide;

and

N-(2-Adamantan-1-yl-ethyl)-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl) benzamide.

30

10. The use of a compound according to any one of claims 1 to 9 in the manufacture of a medicament for treating a condition selected from the group consisting of arthritis (including psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and acute synovitis), inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, adult respiratory distress syndrome, asthma, bronchitis chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, allergic reactions, allergic contact hypersensitivity, eczema, contact dermatitis, psoriasis, sunburn, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, bone resorption disease, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, neurotrauma, spinal cord injury, neuro-degenerative disorders, Alzheimer's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, corneal scarring, scleritis, abnormal wound healing, burns, autoimmune disorders, Huntington's disease, diabetes, AIDS, cachexia, sepsis, septic shock, endotoxic shock, conjunctivitis shock, gram negative sepsis, toxic shock syndrome, cerebral malaria, cardiac and renal reperfusion injury, thrombosis, glomerularonephritis, graft vs. host reaction, allograft rejection, organ transplant toxicity, ulcerative colitis, or muscle degeneration, in a mammal.

35

11. The use according to claim 10 wherein the condition is selected from the group consisting of psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and acute synovitis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, adult respiratory distress syndrome, asthma, bronchitis chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, psoriasis, and ulcerative colitis.

40

12. A pharmaceutical composition for the treatment of a P2X₇ mediated disease in a mammal which comprises a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

45

13. A compound according to any one of claims 1 to 9 for use in treating a condition selected from the group consisting of arthritis (including psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella

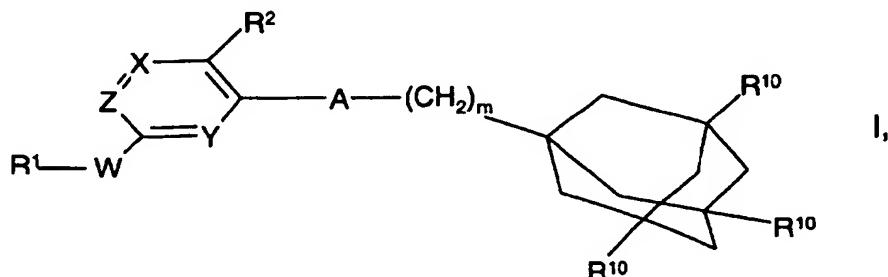
5 arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and acute synovitis), Inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, adult respiratory distress syndrome, asthma, bronchitis chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, allergic reactions, allergic contact hypersensitivity, eczema, contact dermatitis, psoriasis, sunburn, cancer, tissue ulceration, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, bone resorption disease, loosening of artificial joint implants, atherosclerosis, aortic aneurysm, congestive heart failure, myocardial infarction, stroke, cerebral ischemia, head trauma, neurotrauma, spinal cord injury, neuro-degenerative disorders, 10 Alzheimer's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, corneal scarring, scleritis, abnormal wound healing, burns, autoimmune disorders, Huntington's disease, diabetes, AIDS, cachexia, sepsis, septic shock, endotoxic shock, conjunctivitis shock, gram negative sepsis, toxic shock syndrome, cerebral malaria, cardiac and renal reperfusion injury, 15 thrombosis, glomerularonephritis, graft vs. host reaction, allograft rejection, organ transplant toxicity, ulcerative colitis, or muscle degeneration, in a mammal.

15 14. A compound according to any one of claims 1 to 9 for use according to claim 13, wherein the condition is selected from the group consisting of psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and acute synovitis, inflammatory bowel disease, Crohn's disease, emphysema, acute respiratory distress syndrome, adult respiratory distress syndrome, asthma, bronchitis chronic obstructive pulmonary disease, chronic pulmonary inflammatory disease, psoriasis, and ulcerative colitis.

20 15. A compound according to any one of claims 1 to 9 for use in medicine.

25 **Patentansprüche**

30 1. Verbindung der Formel



45 worin

A für -(C=O)NH- oder -NH(C=O)- steht;

X, Y und Z für =(CR³)-, =(CR⁴)- und =(CR⁵)- oder für =N-, =(CR⁴)- und =(CR⁵)- oder für =(CR³)-, =N- und =(CR⁵)- oder für =(CR³)-, =(CR⁴)- und =N- oder für =N-, =(CR⁴)- und =N- oder für =(CR³)-, =N- und =N- oder für =N-, =N- und =(CR⁵)- stehen;

50 W eine Bindung darstellt oder für -O-, >(C=O), -(CH₂)_o-, -(CH=CH)-, -C≡C-, -(CH₂)_oO-, -O(CH₂)_o-, -O(CH₂)_pO-, -O(CH₂)_qO(CH₂)_r-, -CR⁶(OH)-, -(CH₂)_oO(CH₂)_r-, -(CH₂)_oO(CH₂)_qO-, >NR⁷, -(CH₂)_oNR⁷-, -NR⁷(CH₂)_o-, -(CH₂)_oNR⁷(CH₂)_r-, -O(CH₂)_pNR⁷-, -O(CH₂)_qNR⁷(CH₂)_r-, -(CH₂)_oNR⁷(CH₂)_qO-, NR⁷(CH₂)_qO-, -NR⁷(CH₂)_qO(CH₂)_r-, -CONR⁷-, -NR⁷CO-, >S(O)_n, -S(O)_nCH₂-, -CH₂S(O)_n-, -SO₂NR⁷- oder -NR⁷SO₂- steht;

55 m eine ganze Zahl von 1 bis 2 bedeutet;

n eine ganze Zahl von 0 bis 2 bedeutet;

o eine ganze Zahl von 1 bis 6 bedeutet;

p eine ganze Zahl von 2 bis 6 bedeutet;

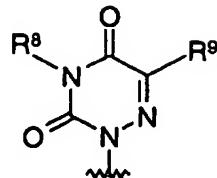
q eine ganze Zahl von 2 oder 3 bedeutet;

r eine ganze Zahl von 1 bis 3 bedeutet;

R¹ die Gruppe

5

10



darstellt, worin

15 R⁸ ausgewählt ist aus Wasserstoff, CF₃-, (C₁-C₆)Alkyl, HO-(C₂-C₆)Alkyl und (C₃-C₈)Cycloalkyl, und R⁹ ausgewählt ist aus Wasserstoff, (C₁-C₆)Alkyl, CF₃-CH₂-, HO-(C₂-C₆)Alkyl und (C₃-C₈)Cycloalkyl; R² ausgewählt ist aus der Gruppe (i) Wasserstoff, (ii) Halogen, (iii) Cyano, (iv) (C₁-C₄)Alkyl, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome, (v) (C₂-C₄)Alkenyl, (vi) (C₂-C₄)Alkynyl und (vii) (C₁-C₄)Alkoxy, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome;

20 R³, R⁴ und R⁵ jeweils unabhängig ausgewählt sind aus der Gruppe (i) Wasserstoff, (ii) Halogen, (iii) Cyano, (iv) Nitro, (v) Amino, (vi) Hydroxy, (vii) (C₁-C₆)Alkyl, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome, (viii) (C₃-C₈)Cycloalkyl, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome; (ix) (C₁-C₆)Alkoxy, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome; und (x) (C₃-C₈)Cycloalkoxy, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome;

25 R⁶ für Wasserstoff oder (C₁-C₆)Alkyl steht;

R⁷ für Wasserstoff, (C₁-C₆)Alkyl oder (C₃-C₈)Cycloalkyl steht;

jeder Rest R¹⁰ unabhängig ausgewählt ist aus Wasserstoff und Halogen; oder ein pharmazeutisch akzeptables Salz oder Solvat davon.

30 2. Verbindung nach Anspruch 1, worin X, Y und Z für =(CR³)-, =(CR⁴)- und =(CR⁵)- stehen.

3. Verbindung nach einem der vorhergehenden Ansprüche, worin einer der Reste R³, R⁴ oder R⁵ ausgewählt ist aus (i) Wasserstoff, (ii) Halogen, (iii) Cyano, (iv) Nitro, (v) Amino, (vi) Hydroxy, (vii) (C₁-C₆)Alkyl, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome, (viii) (C₃-C₈)Cycloalkyl, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome, (ix) (C₁-C₆)Alkoxy, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome, und (x) (C₃-C₈)Cycloalkoxy, optional substituiert durch 1 bis 4 Chlor- oder Fluoratome.

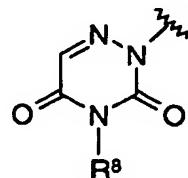
35 4. Verbindung nach einem der vorhergehenden Ansprüche, worin m für 1 steht.

5. Verbindung nach einem der vorhergehenden Ansprüche, worin A für -(C=O)NH-steht.

6. Verbindung nach den Ansprüchen 1 bis 5, worin R¹ für

45

50



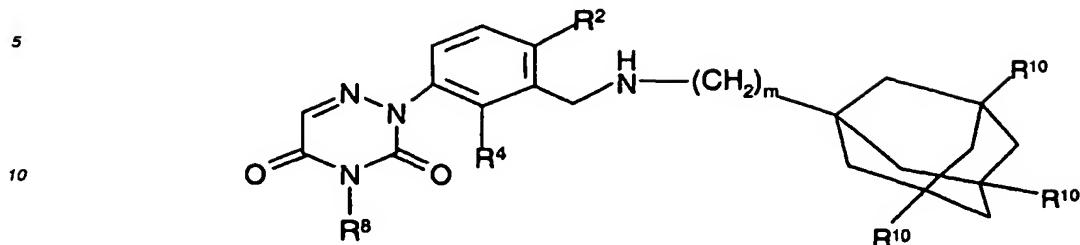
I

55

steht, worin R⁸ ausgewählt ist aus Wasserstoff und (C₁-C₆)Alkyl.

7. Verbindung nach einem der vorhergehenden Ansprüche, worin W eine Bindung darstellt.

8. Verbindung nach Anspruch 1, die die Formel



aufweist, worin

m die ganze Zahl 1 oder 2 bedeutet,

R² für Fluor oder Chlor steht,

R⁴ ausgewählt ist aus Wasserstoff, Halogen, Cyano, Hydroxy, (C₁-C₃)Alkyl, (C₃-C₆)Cycloalkyl, (C₁-C₃)Alkoxy, -CF₃, -OCF₃ und (C₃-C₆)Cycloalkoxy;

R⁸ für ein Wasserstoffatom oder (C₁-C₆)Alkyl, CF₃-CH₂- oder HO-(C₂-C₆)Alkyl oder (C₃-C₈)Cycloalkyl steht;

R¹⁰ für Wasserstoff oder Fluor steht;

oder deren pharmazeutisch akzeptables Salz oder Solvat.

9. Verbindung, die ausgewählt ist aus:

30 N-Adamantan-1-ylmethyl-2-chlor-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamid;

N-Adamantan-1-ylmethyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-methyl-benzamid;

N-Adamantan-1-ylmethyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-fluor-benzamid;

35 N-Adamantan-1-ylmethyl-2-chlor-5-(4-methyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamid;

2-Chlor-N-(3,5-difluor-adamantan-1-ylmethyl)-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamid; und

40 N-(2-Adamantan-1-yl-ethyl)-2-chlor-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamid.

45 10. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 9 zur Herstellung eines Arzneimittels zur Behandlung eines Zustands, der ausgewählt ist aus Arthritis (einschließlich Psoriasisarthritis, Reiter-Krankheit, rheumatoider Arthritis, Gicht, traumatischer Arthritis, Röteln-Arthritis, rheumatoider Spondylitis, Osteoarthritis, Arthritis urica (gouty arthritis) und akuter Synovitis), entzündlichen Darmerkrankungen, Morbus Crohn, Emphysem, akutem Atemnotsyndrom, Atemnotsyndrom des Erwachsenen (adult respiratory distress syndrome), Asthma, Bronchitis, chronischer obstruktiver Lungenerkrankung (chronic obstructive pulmonary disease), chronischen entzündlichen Lungenerkrankungen, Silicose, Lungensarkoidose, allergischen Reaktionen, allergischer Kontakthypersensibilität, Ekzemen, Kontaktdermatitis, Psoriasis, Sonnenbrand, Krebs, Geschwürbildung in Geweben, Restenose, Parodontitis, Epidermolysis bullosa, Osteoporose, Krankheiten mit erhöhter Knochenresorption, Lockerung künstlicher Gelenkimplantate, Atherosklerose, Aorten-Aneurysma, dekompensierter Herzinsuffizienz, Myocardinfarkt, Schlaganfall, zerebraler Ischämie, Schädeltrauma, Neurotrauma, Verletzungen des Rückenmarks, neurodegenerativen Störungen, Alzheimer, Parkinson, Migräne, Depression, peripherer Neuropathie, Schmerzen, zerebraler Amyloidangiopathie, nootrope oder Wahrnehmungs-Enhancement (nootropic or cognition enhancement), amytotropher Lateralsklerose, multipler Sklerose, okulärer Angiogenesis, Verletzungen der Hornhaut, Degeneration der Macula, Vernarbung der Hornhaut, Scleritis, abnormaler Wundheilung, Verbrennungen, Autoimmunkrankheiten, Chorea Huntington, Diabetes, AIDS, Cachexie, Sepsis, septischem Schock, Endotoxinschock, Conjunctivitis-Schock, Sepsis durch gram-negative Erreger, toxischem Schocksyndrom, Malaria cerebralis, Verletzung bei Herz- und Nieren-Reperfusion, Thrombose, Glomerulonephritis, Transplantat-Wirt-Reaktion, Allotransplantat-Absto-

Bung, Toxizität nach Organtransplantation, Colitis ulcerosa oder Muskeldegeneration bei Säugetieren.

11. Verwendung nach Anspruch 10, wobei der Zustand ausgewählt ist aus der Gruppe bestehend aus Psoriasisarthritis, Reiter-Krankheit, Gelenkrheumatismus, Gicht, traumatischer Arthritis, Rötel-Arthritis, Morbus Bechterew, 5 Osteoarthritis, Arthritis urica und akuter Synovitis.

12. Pharmazeutische Komposition zur Behandlung von durch P2X₇ vermittelten Krankheiten bei Säugetieren, enthaltend eine Verbindung nach einem der Ansprüche 1 bis 9 und einen pharmazeutisch akzeptablen Träger.

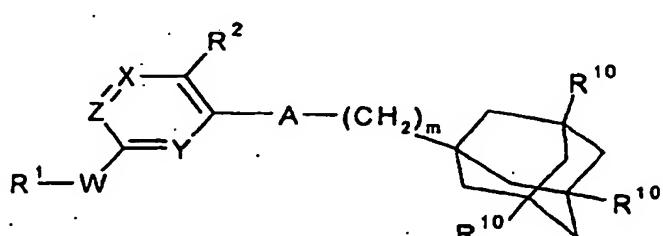
13. Verbindung nach einem der Ansprüche 1 bis 9 zur Verwendung zur Behandlung eines Zustands, der ausgewählt ist aus Arthritis (einschließlich Psoriasisarthritis, Reiter-Krankheit, rheumatoider Arthritis, Gicht, traumatischer Arthritis, Rötel-Arthritis, rheumatoider Spondylitis, Osteoarthritis, Arthritis urica und akuter Synovitis), entzündlichen Darmerkrankungen, Morbus Crohn, Emphysem, akutem Atemnotsyndrom, Atemnotsyndrom des Erwachsenen (ARDS), Asthma, Bronchitis, chronischer obstruktiver Lungenerkrankung (COPD), chronischen entzündlichen 15 Lungenerkrankungen, Silicose, Lungsarkoidose, allergischen Reaktionen, allergischer Kontakthypersensibilität, Ekzemen, Kontaktdermatitis, Psoriasis, Sonnenbrand, Krebs, Geschwürbildung in Geweben, Restenose, Parodontitis, Epidermolysis bullosa, Osteoporose, Krankheiten mit erhöhter Knochenresorption, Lockerung künstlicher Gelenkimplantate, Atherosklerose, Aorten-Aneurysma, dekompensierter Herzinsuffizienz, Myocardinfarkt, 20 Schlaganfall, zerebraler Ischämie, Schädeltrauma, Neurotrauma, Verletzungen des Rückenmarks, neurodegenerativen Störungen, Alzheimer, Parkinson, Migräne, Depression, peripherer Neuropathie, Schmerzen, zerebraler Amyloidangiopathie (CAA), nootrope oder Wahrnehmungs-Enhancement, amyotropher Lateralsklerose, multipler Sklerose, okulärer Angiogenese, Verletzungen der Hornhaut, Degeneration der Macula, Vernarbung der Hornhaut, Scleritis, abnormaler Wundheilung, Verbrennungen, Autoimmunkrankheiten, Chorea Huntington, Diabetes, AIDS, 25 Cachexie, Sepsis, septischem Schock, Endotoxinschock, Conjunctivitis-Schock, Sepsis durch gram-negative Erreger, toxischem Schocksyndrom, Malaria cerebralis, Verletzung bei Herz- und Nieren-Reperfusion, Thrombose, Glomerulonephritis, Transplantat-Wirt-Reaktion, Allotransplantat-Abstoßung, Toxizität nach Organtransplantation, Colitis ulcerosa oder Muskeldegeneration bei Säugetieren.

14. Verbindung nach einem der Ansprüche 1 bis 9 zur Verwendung gemäß Anspruch 13, wobei der Zustand ausgewählt ist aus Psoriasisarthritis, Reiter-Krankheit, Gelenkrheumatismus, Gicht, traumatischer Arthritis, Rötel-Arthritis, Morbus Bechterew, Osteoarthritis, Arthritis urica und akuter Synovitis, entzündlichen Darmerkrankungen, Morbus Crohn, Emphysem, akutem Atemnotsyndrom, Atemnotsyndrom des Erwachsenen (ARDS), Asthma, Bronchitis, chronischer obstruktiver Lungenerkrankung (COPD), chronischen entzündlichen Lungenerkrankungen, Psoriasis, und Colitis ulcerosa.

35 15. Verbindung nach einem der Ansprüche 1 bis 9 zur Verwendung in der Medizin.

Revendications

40 1. Composé de formule



55

dans laquelle :

A représente -(C=O)NH- ou -NH(C=O)- ;

X, Y et Z représentent =(CR³)-, =(CR⁴)- et =(CR⁵)- ; ou =N- , =(CR⁴)- et =(CR⁵)- ; ou =(CR³)-, =N- et =(CR⁵)- ;

EP 1 310 493 B1

ou $=(CR^3)-$, $=(CR^4)-$ et $=N-$; ou $=N-$, $=(CR^4)-$ et $=N-$; ou $=(CR^3)-$, $=N-$ et $=N-$; ou $=N-$, $=N-$ et CR^5 , respectivement ;
 W représente une liaison, $-O-$, $>(C=O)$, $-(CH_2)_o-$, $-(CH=CH)-$, $-C\equiv C-$, $-(CH_2)_pO-$, $-O(CH_2)_o-$, $-O(CH_2)_pO-$, $-O(CH_2)_qO(CH_2)_r-$,
 $(CH_2)_qO(CH_2)_r-$, $-CR^6(OH)-$, $-(CH_2)_rO(CH_2)_r-$, $-(CH_2)_rO(CH_2)_qO-$, $>NR^7$, $-(CH_2)_oNR^7-$, $-NR^7(CH_2)_o-$, $-(CH_2)_rNR^7$
 $(CH_2)_r-$, $-O(CH_2)_pNR^7-$, $-O(CH_2)_qNR^7(CH_2)_r-$, $-(CH_2)_rNR^7(CH_2)_qO-$, $-NR^7(CH_2)_qO-$, $-NR^7(CH_2)_qO(CH_2)_r-$,
 $-CONR^7-$, $-NR^7CO-$, $>S(O)_n$, $-S(O)_nCH_2-$, $-CH_2S(O)_n-$, $-SO_2NR^7-$ ou $-NR^7SO_2-$;

5 m représente un entier de 1 à 2 ;

n représente un entier de 0 à 2 ;

o représente un entier de 1 à 6 ;

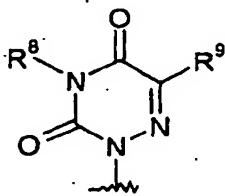
10 p représente un entier de 2 à 6 ;

q représente un entier de 2 à 3 ;

r représente un entier de 1 à 3 ;

R¹ représente le groupe

15



20

25 où R⁸ est sélectionné dans le groupe consistant en l'hydrogène, CF_3- , un groupe alkyle en C_1-C_6 , HO -(alkyle en C_2-C_6) ou cycloalkyle en C_3-C_8 ,

où R⁹ est sélectionné dans le groupe consistant en l'hydrogène, et les groupes alkyle en C_1-C_6 , CF_3-CH_2- , HO -(alkyle en C_2-C_6) ou cycloalkyle en C_3-C_8 .

30 R² est sélectionné dans le groupe consistant en (i) l'hydrogène, (ii) les halogènes, (iii) cyano, (iv) alkyle en C_1-C_4 facultativement substitué par de un à quatre chloro ou fluoro, (v) alkényle en C_2-C_4 ; (vi) alkynyle en C_2-C_4 et (vii) (alkyle en C_1-C_4)oxy facultativement substitué par de un à quatre chloro ou fluoro ;

R³, R⁴ et R⁵ sont chacun indépendamment sélectionnés dans le groupe consistant en (i) l'hydrogène, (ii) les halogènes, (iii) cyano, (iv) nitro, (v) amino, (vi) hydroxyle, (vii) alkyle en C_1-C_6 facultativement substitué par de un à quatre chloro ou fluoro, (viii) cycloalkyle en C_3-C_8 facultativement substitué par de un à quatre chloro ou fluoro, (ix) (alkyle en C_1-C_6)oxy facultativement substitué par de un à quatre chloro ou fluoro, et (x) (cycloalkyle en C_3-C_8)oxy facultativement substitué par de un à quatre chloro ou fluoro ;

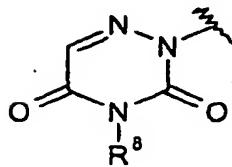
35 R⁶ représente l'hydrogène ou alkyle en C_1-C_6 ;

R⁷ représente l'hydrogène, alkyle en C_1-C_6 ou cycloalkyle en C_3-C_8 ;

chaque R¹⁰ est indépendamment sélectionné dans le groupe consistant en l'hydrogène ou halogéno ;

40 ou un sel pharmaceutiquement acceptable ou un solvate d'un tel composé.

2. Composé selon la revendication 1, dans lequel X, Y et Z représentent respectivement $=(CR^3)-$, $=(CR^4)-$ et $=(CR^5)-$.
3. Composé selon l'une quelconque des revendications précédentes dans lequel l'un de R³, R⁴ ou R⁵ est sélectionné dans le groupe consistant en (i) l'hydrogène, (ii) halogéno, (ii) cyano, (iii) nitro, (iv) amino, (v) hydroxyle, (vi) alkyle en C_1-C_6 facultativement substitué par de un à quatre chloro ou fluoro, (vii) cycloalkyle en C_3-C_8 facultativement substitué par de un à quatre chloro ou fluoro, (viii) (alkyle en C_1-C_6)oxy facultativement substitué par de un à quatre chloro ou fluoro et (ix) (cycloalkyle en C_3-C_8)oxy facultativement substitué par de un à quatre chloro ou fluoro.
4. Composé selon l'une quelconque des revendications précédentes dans lequel m représente 1.
5. Composé selon l'une quelconque des revendications précédentes dans lequel A représente $-(C=O)NH-$.
- 55 6. Composé selon les revendications 1 à 13 dans lequel R¹ représente



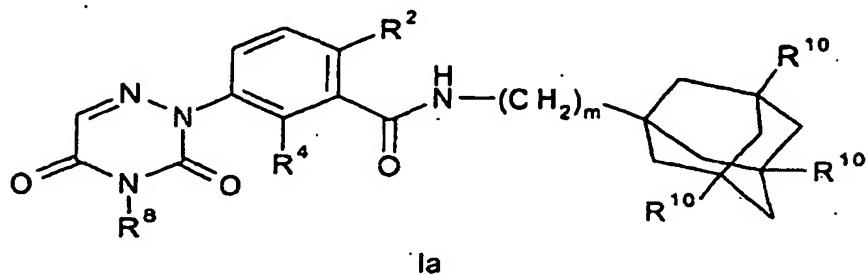
10 où R⁸ est sélectionné dans le groupe consistant en l'hydrogène et alkyle en C₁-C₆.

7. Composé selon l'une quelconque des revendications précédentes dans lequel W est une liaison.

8. Composé selon la revendication 1 dans lequel ledit composé de formule I a la formule

15

20



25

30

dans laquelle

m est un entier allant de 1 à 2 ;

R² représente fluoro ou chloro ;

R⁴ est sélectionné dans le groupe consistant en l'hydrogène, halogéno, cyano, hydroxylique, alkyle en C₁-C₃, cycloalkyle en C₃-C₆, (alkyle en C₁-C₃)oxy, -CF₃, -OCF₃ et (cycloalkyle en C₃-C₆)oxy ;

35

R⁸ est un atome d'hydrogène ou un groupe alkyle en C₁-C₆, CF₃-CH₂- , HO-(alkyle en C₂-C₆)- ou cycloalkyle en C₃-C₈ ;

R¹⁰ représente l'hydrogène ou fluoro ;

ou un sel pharmaceutiquement acceptable ou un solvate d'un tel composé.

40

9. Composé sélectionné dans le groupe consistant en :

le N-adamantan-1-ylméthyl-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide ;

le N-adamantan-1-ylméthyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-méthyl-benzamide ;

le N-adamantan-1-ylméthyl-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-2-fluoro-benzamide ;

45

le N-adamantan-1-ylméthyl-2-chloro-5-(4-méthyl-3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide ;

le 2-chloro-N-(3,5-difluoro-adamantan-1-ylméthyl)-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide ; et

le N-(2-adamantan-1-yl-éthyl)-2-chloro-5-(3,5-dioxo-4,5-dihydro-3H-[1,2,4]triazin-2-yl)-benzamide.

50

10. Utilisation d'un composé selon l'une quelconque des revendications 1 à 9 dans la fabrication d'un médicament pour le traitement d'un état sélectionné dans le groupe consistant en l'arthrite (y compris l'arthrite psoriasique, le syndrome de Reiter, l'arthrite rhumatoïde, la goutte, l'arthrite traumatique, l'arthrite associée à la rubéole, la spondylite rhumatoïde, l'ostéoarthrite, l'arthrite goutteuse et la synovite aiguë), la maladie inflammatoire de l'intestin, la maladie de Crohn, l'emphysème, le syndrome de détresse respiratoire aiguë, le syndrome de détresse respiratoire de l'adulte, l'asthme, la bronchite, la maladie pulmonaire obstructive chronique, la maladie inflammatoire pulmonaire chronique, la silicose, la sarcopidose pulmonaire, les réactions allergiques, l'hypersensibilité de contact allergique, l'eczéma, la dermatite de contact, le psoriasis, l'érythème solaire, le cancer, l'ulcération des tissus, la resténose, la maladie périodontale, l'épidermolyse bulleuse, l'ostéoporose, la maladie de la résorption osseuse,

le relâchement d'implants d'articulations artificielles, l'athérosclérose, l'anévrisme aortique, l'insuffisance cardiaque congestive, l'infarctus du myocarde, les accidents cérébro-vasculaires, l'ischémie cérébrale, les traumatismes de la tête, les traumatismes neurologiques, les lésions de la moelle épinière, les maladies neuro-dégénératives, la maladie de Alzheimer, la maladie de Parkinson, la migraine, la dépression, la neuropathie périphérique, la douleur, l'angiopathie amyloïde cérébrale, l'amélioration nootropique ou de la conscience, la sclérose latérale amyotrophique, la sclérose en plaques, l'angiogénèse oculaire, les lésions de la cornée, la dégénérescence maculaire, la tâie de la cornée, la sclérite, la cicatrisation anormale des plaies, les brûlures, les maladies auto-immunes, la maladie de Huntington, le diabète, le SIDA, la cachexie, la sepsis, le choc septique, le choc endotoxique, la conjonctivite de choc, la sepsis à Gram-négatifs, le syndrome de choc toxique, la malaria cérébrale, les lésions de reperfusion rénales et cardiaques, la thrombose, la glomérulonéphrite, les réactions de greffes vis-à-vis de l'hôte, les rejets d'allograftes, la toxicité de la transplantation d'organes, la colite ulcérante, ou la dégénérescence musculaire, chez un mammifère.

5 11. Utilisation selon la revendication 10, dans laquelle l'état est sélectionné dans le groupe consistant en l'arthrite psoriasique, le syndrome de Reiter, l'arthrite rhumatoïde, la goutte, l'arthrite traumatique, l'arthrite associée à la rubéole, la spondylite rhumatoïde, l'ostéoarthrite, l'arthrite goutteuse et la synovite aiguë, la maladie inflammatoire de l'intestin, la maladie de Crohn, l'emphysème, le syndrome de détresse respiratoire aiguë, le syndrome de détresse respiratoire de l'adulte, l'asthme, la bronchite, la maladie pulmonaire obstructive chronique, la maladie inflammatoire pulmonaire chronique, la psoriasis et la colite ulcérante.

10 12. Composition pharmaceutique pour le traitement d'une maladie médiaée par P2X₇, chez un mammifère, qui comprend un composé selon l'une quelconque des revendications 1 à 9 et un support pharmaceutiquement acceptable.

15 13. Composé selon l'une des revendications 1 à 9 pour une utilisation dans le traitement d'un état sélectionné dans le groupe consistant en l'arthrite psoriasique, le syndrome de Reiter, l'arthrite rhumatoïde, la goutte, l'arthrite traumatique, l'arthrite associée à la rubéole, la spondylite rhumatoïde, l'ostéoarthrite, l'arthrite goutteuse et la synovite aiguë, la maladie inflammatoire de l'intestin, la maladie de Crohn, l'emphysème, le syndrome de détresse respiratoire aiguë, le syndrome de détresse respiratoire de l'adulte, l'asthme, la bronchite, la maladie pulmonaire obstructive chronique, la maladie inflammatoire pulmonaire chronique, la silicose, la sarcoidose pulmonaire, les réactions allergiques, l'hypersensibilité de contact allergique, l'eczéma, la dermatite de contact, le psoriasis, l'erythème solaire, le cancer, l'ulcération des tissus, la resténose, la maladie périodontale, l'épidermolyse bulleuse, l'ostéoporose, la maladie de la résorption osseuse, le relâchement d'implants d'articulations artificielles, l'athérosclérose, l'anévrisme aortique, l'insuffisance cardiaque congestive, l'infarctus du myocarde, les accidents cérébro-vasculaires, l'ischémie cérébrale, les traumatismes de la tête, les traumatismes neurologiques, les lésions de la moelle épinière, les maladies neuro-dégénératives, la maladie de Alzheimer, la maladie de Parkinson, la migraine, la dépression, la neuropathie périphérique, la douleur, l'angiopathie amyloïde cérébrale, l'amélioration nootropique ou de la conscience, la sclérose latérale amyotrophique, la sclérose en plaques, l'angiogénèse oculaire, les lésions de la cornée, la dégénérescence maculaire, la tâie de la cornée, la sclérite, la cicatrisation anormale des plaies, les brûlures, les maladies auto-immunes, la maladie de Huntington, le diabète, le SIDA, la cachexie, la sepsis, le choc septique, le choc endotoxique, la conjonctivite de choc, la sepsis à Gram-négatifs, le syndrome de choc toxique, la malaria cérébrale, les lésions de reperfusion rénales et cardiaques, la thrombose, la glomérulonéphrite, les réactions de greffes vis-à-vis de l'hôte, les rejets d'allograftes, la toxicité de la transplantation d'organes, la colite ulcérante, ou la dégénérescence musculaire, chez un mammifère.

20 14. Composé selon l'une des revendications 1 à 9 pour une utilisation selon la revendication 13, dans laquelle l'état est sélectionné dans le groupe consistant en l'arthrite psoriasique, le syndrome de Reiter, l'arthrite rhumatoïde, la goutte, l'arthrite traumatique, l'arthrite associée à la rubéole, la spondylite rhumatoïde, l'ostéoarthrite, l'arthrite goutteuse et la synovite aiguë, la maladie inflammatoire de l'intestin, la maladie de Crohn, l'emphysème, le syndrome de détresse respiratoire aiguë, le syndrome de détresse respiratoire de l'adulte, l'asthme, la bronchite, la maladie pulmonaire obstructive chronique, la maladie inflammatoire pulmonaire chronique, la psoriasis, et la colite ulcérante.

25 15. Composé selon l'une quelconque des revendications 1 à 9 pour une utilisation en médecine.